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Following the death of the Editor in November, Professor Elis Berven will act in this capacity until the next meeting, in June 1951, of the Northern Association for Medical Radiology, when a new appointment will be made.

Gösta Forssell

* 2. III. 1876 † 13. XI. 1950

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GÖSTA FORSSELL

In Memoriam

Words of remembrance at the meeting of the Swedish Medical Association, Nov. 21st 1950

When GÖSTA FORSSELL, pioneer and organizer, scientist and teacher, healer and lover of mankind, passed away on Monday, the 13th of November, after several months of increasing heart failure Sweden lost one of the most noble of Her sons.

His figure as a leader, his innate living strength and his indefatigable energy were, no doubt, inheritances from the generations of Dalecarlian and Helsingland farmers, warriors and clergy — authoritative and resolute forefathers from which he could trace his descent right back from the sixteenth century.

FORSSELL's richly facetted personality, his burning bent on research and marked scientific powers, his constructive imagination as well as his organizing capabilities were probably those qualities which caused him, whilst still in his years of study, to throw himself into an entirely new branch of medicine — radiology — which the discoveries of roentgen and radium rays had created. His powers of bold intuition enabled him to realize the enormous developmental possibilities of this science and its future importance for medicine.

As a young medical student he served his apprenticeship under the first roentgen pioneer in Sweden, THOR STENBECK. About this time (1899) he took part in the first curative treatment in the world of a case of cancer of the skin. One hundred and fifty treatments extending over some nine months were required in all for the cure. The patient was demonstrated nearly 30 years later free from symptoms at the second International Congress of Radiology in Stockholm. One may perhaps best appreciate the progress of development when I state that a similar

case in these days would be cleared up by a single treatment lasting but a minute.

The outlines of FORSSELL's radiological activities are as follows: Assistant in the Roentgen Department of the University Hospital of Upsala, 1902. Head of the Roentgen Institute of the Serafimerlasarettet 1906—1941. Director of the »Radiumhemmet» (Radium Home) 1910—1926. Professor of Medical Radiology at the Karolinska Institutet from 1917 to 1936, when the professorship was divided in two: Roentgen-diagnosis and Radiotherapy; he was then professor of Roentgen Diagnosis from 1936 until 1941, in which year he retired. Within this simple framework is enclosed a life's work of great dimensions.

FORSSELL faithfully devoted his whole power of organization to the development of medical radiology. His great achievement as the pioneer of this science lies in the fact that he was able to develop it into an independent branch of medicine on a par with the other specialities. Previously there had been a tendency, more especially in Germany, to establish smaller radiological departments in various medical, surgical, etc., clinics with the radiologist as an assistant to the head of the clinic. FORSSELL realized the danger of this disintegration and that the only road to sound development lay in the centralization of radiology, diagnostic as well as therapeutic in large well-equipped independent departments with their own organization, doctors and nurses. He exercised all his strength to accomplish this in Sweden.

FORSSELL had the good fortune to see his plan realized to an undreamt-of degree when the organization of Swedish radiology thereafter has served as a pattern in many countries.

The little roentgen room at the Serafimerlasarettet, where FORSSELL began to work independently from 1906 assisted by only one nurse, has been developed by him and by his pupils into the two roentgen diagnostic institutions at the Serafimer and Caroline Hospitals: the noteworthy planning, organization and scientific output of these, has placed them in the very front rank of similar institutions.

Roentgen diagnosis has developed and assumed such importance during five decades that it may be said that no clinical diagnosis is made without a previous roentgen examination. From the simple recording of the form and structure of an organ, it has grown into one of the most important of all medicine's sources of information of the function of the organ in normal and pathological conditions. Roentgen anatomy, roentgen physiology and roentgen pathology continually proceed forwards.

The development of radiotherapy has been very similar. The little trial hospital Radiumhemmet of 1910 with its sixteen beds, single roentgen apparatus and 120 mg of radium, and which was established with

the aid of private contributions, has developed under FORSSELL's far-sighted guidance into King Gustav V:s Jubilee Clinic at the Karolinska Sjukhuset with its three sections: Radiumhemmet, the Institute of Radiophysics, and the Institute of Radiopathology. The design and organization of these has been a pattern for the Jubilee Clinics in Lund and Göteborg and others.

A steady stream of foreign doctors pass every year through these radiological institutions in order to study their organization, methods of work and their results.

The progress of radiology in Sweden during FORSSELL's time is apparent from the fact that we now have some seventy radiological departments in the big hospitals with directors of consultant status, most of them trained by FORSSELL and his pupils.

It was after FORSSELL in 1912 had given his, what has become, classical address on the radium treatment of carcinoma of the uterus and shown that seriously sick women, although inoperable could in a great percentage of cases be considerably improved, and a number even be rendered free of signs, that the Municipal Council of the City of Stockholm made a grant from the Forsgrénska Fund of half a million Swedish Crowns to the Radiumhemmet. Queen Victoria headed a collection which likewise brought in a similar sum. Numerous patients have also given generous subscriptions to the Cancer Association in gratitude for their satisfactory treatment. FORSSELL took an active part in a collection on the occasion of King Gustaf V's seventieth birthday and he drew up plans concerning the use of the money with great care. As is known, the Cancer Association and the Jubilee Fund have shared in the costs of the building, equipment &c. of the three Jubilee Clinics to the extent of seven millions.

The burden of work in planning the Karolinska Sjukhuset was born almost entirely by the triumvirate, FORSSELL, KEY and WESTMAN. The final steering of the Karolinska Sjukhuset into haven, and the collaboration with the City of Stockholm for the preparation of the accommodation of medical training at the new City hospital at Sabbatsberg, could in a great measure have been realised only by FORSSELL's power of diplomacy and ability to unite widely different opinions for the solution of these questions.

FORSSELL's organizing ability was yet of use in other fields. He was secretary of the Cancer Association in Stockholm from 1910 to 1926 and its President from 1926 to 1936, a member of the Board of King Gustaf V's Jubilee Fund from 1928 and President of the Swedish Medical Association in 1931—1932. He further founded the Swedish Association for Medical Radiology and the Society of Swedish Radiologists and was for some years their President. After the first world war he succeeded in

bringing the radiologists of the Northern lands together into the Northern Association for Medical Radiology in 1919. The Scandinavian radiologists had up to that time published their scientific communications in the large international journals, a fact which did not permit of a complete survey of the scientific production of the North. FORSSELL therefore founded *Acta Radiologica* and has been its editor-in-chief until the time of his death. The thirty-four published volumes give a fair insight into Northern radiological research and have also actively participated in the reputation and appreciation which this research enjoys everywhere.

FORSSELL took part in the first international congress of Radiology in London in 1925. The transfer of the second world congress to Stockholm in 1928 was an acknowledgement of FORSSELL and Swedish radiology; it ran a resplendent course. I need only here recall the memorable demonstration before the Congress of a hundred patients permanently cured of cancer after radiological treatment, and which was accepted as a justifiable homage to FORSSELL's work.

As inspector for fifteen years of the Medical Students Association he put work full of interest and value into the service and as inspector for many years of his old school, Norra Latin, he started among other activities, the formation of its summer home, which served as a pattern for several similar homes for other schools. He was a warm friend of youth, and sought to further its welfare in every way.

FORSSELL's success as a breaker of new ground and as an organizer depended upon the extreme wisdom and objectivity, thoroughness and unselfishness with which he worked out his proposals and the clear and logical form in which they were presented. His advice to the young ran: »Never propound a proposition if you be doubtful of the possibility of carrying it through!» He conducted the fight for his conceptions with edged weapons and raised visor.

In order to understand how FORSSELL still had the time, in spite of the terrific burden of the work of organization, for the comprehensive work of research and teaching both in diagnosis and therapy and which placed him among the foremost in his science, one must have known his burning desire for research.

FORSSELL himself says the following on the goal and importance of research: »Research is the seeking of truth, the finding out of how Nature herself solves those problems which array themselves before human beings. To be able to put questions to Nature and glean her answers, to take counsel from Nature is the highest privilege of mankind. By research, that is to say, by the power which brilliantly gifted human beings possess of listening to Nature, we have attained to the knowledge, the accomplishments, and the means by which the culture of Man has been built up.»

During the difficult economic times which followed the first world war, FORSSELL took the initiative in forming the Association for Medical Research which would be able to give important contributions for research. Upon his sixtyfifth birthday, he received a present of over 100,000 crowns — Gösta Forssell's Research Fund — the yearly proceeds of which entirely go to the support of research.

FORSSELL's scientific works are characterized by being full of original suggestions, and showing sound mental acumen and a logical and inspiring power of description. They comprise more than 200 works covering the most diverse fields in radiology and closely allied sciences and have given him a name which will never fade. Professor ÅKERLUND gives later a special resumé of FORSSELL's diagnostic works.

FORSSELL's works have perhaps played an even greater rôle in the development of therapy than in diagnosis. I have already mentioned his address to the Swedish Medical Association in 1912 on the treatment of cancer of the uterus which gradually brought about the present conditions when nearly all cases of this disease are treated by roentgen or radium. In a number of the other works he has given an account of the methods and results in the treatment of cancer in various situations. His foremost work however »on the permanency of radiological healing» is a synopsis of the permanence of healing after treatment by irradiation. He here shows that once a healing is effected it is as permanent as after, for example, surgical treatment. Thanks to this, treatment by irradiation obtained an anchorage for its further development.

FORSSELL entertained a warm interest for the development of teaching. He took up this question in 1925 at the meeting of the Northern Association for Medical Radiology in Helsingfors, and again in 1928 at the International Congress of Radiology in Stockholm. FORSSELL has actively ensured, by his profound analysis of the necessity for the teaching of radiology, of the means and of the goal, that it is taken up as an independent teaching subject at most universities. He himself possessed eminent talents as a teacher, perhaps most appreciated in his more immediate circles. His analysis of roentgenograms or of a clinical case was fascinating and his juxtaposition of details into a clinical entity, brilliant. He put in devoted work in the training of his assistants and few like him were able to stimulate his pupils to scientific work. He was also their fatherly friend, who ever sought to help them in all the ups and downs of life.

FORSSELL's activity as a doctor, lies on the same level as his work in the field of organization and research. During the course of years he was attracted more and more by suffering human beings and their problems. He gained his patient's unbounded confidence by his impressive personality, by his personal skill in diagnosis and planning and above all by the often difficult and trying radiological treatments. He has been blessed

in thousands of hearts and thanked for all the love, deep understanding and devotion which he perpetually offered his patients in their fight against disease and death.

The distinctions which FORSSELL has been awarded are legion ... honorary membership of nearly all radiological societies, honorary degrees, gold medals, dedicated publications, invitations as guest speaker &c. He was only this summer elected an Honorary Fellow of the Royal Society of Medicine, London, a special distinction.

The mark of honour however upon which he probably set most value, was the command to pay homage and thanks from the Swedish people to the King at the celebrations at the Stadium on the occasion of King Gustaf V's eightieth birthday. His soul-stirring address ended with the words: »King of the People and King of Peace — thus is Thy name on the lips of the people.»

GÖSTA FORSSELL is no more. But as the great man of uncommon stature that he was, his work will endure and bear witness for coming generations of his contribution to the development of Swedish culture.

Elis Berven.

A SHORT REVIEW OF GÖSTA FORSSELL's WORKS IN RADIOTHERAPY AND OTHER SUBJECTS EXCEPTING ROENTGEN DIAGNOSIS

It is impossible in a short article to present an adequate survey of FORSSELL's works. In what follows I can but only try to indicate some of the more important parts of his scientific works. FORSSELL has himself during his lifetime collected together his bibliography, which is published in Acta Radiologica Vol. XXXII (1949) and to which I would refer my readers. His works may be divided into the following parts:

1. Roentgen diagnosis (see pages 440—448)
2. Radiotherapy
3. Electrotherapy
4. Statistics
5. The organizing of the fight against cancer
6. Teaching
7. Hospital construction and organization
8. Biographies and bibliographies
9. Life assurance.

Radiotherapy

FORSSELL's first work in the field of radiotherapy is a report (1904) of *Recent experiences in roentgentherapy*, which gives an interesting insight into the childhood of roentgentherapy. For this reason I give an account of its contents in some detail.

He called attention to the fact that in the year 1900 KIENBÖCK and SCHOLZ showed that »roentgen rays and not ultra-violet rays are the essential active media in the production of the changes in irradiated tissue and that the reaction to irradiation depends directly upon the amount of the roentgen rays absorbed». This is now an obvious reality although then much in dispute.

He gives an account of HOLZKNECHT's chromoradiometer (1902) based upon the ability of roentgen radiation to colour barium salts, and

of the dose *H* which HOLZKNECHT proposed, this being three times the amount of radiation required to produce a slight skin reaction. FORSSELL drew attention to all the difficulties of exact dosage by reason of the inconstancy of the roentgen apparatus and tube (which he generally referred to as a »lamp»!), the latent time and the »idiosyncrasies of the skin» (as for example in psoriasis). He discusses the pros and cons for the use of soft or hard radiation and whether these already observed signs of radiation sickness could be of a »psychic nature or caused by a direct radiation effect».

The four acute reactions (HOLZKNECHT) he described as 1) Complete epilation, 2) Ordinary inflammation with irritation, 3) The creation of painful blistering and 4) Gangrenous dermatitis with destruction of all the skin layers. The initial erythema (*Früh-Erythema*) was considered to be caused by rays »still undiscovered and essential different from roentgen rays». The degrees of chronic roentgen dermatitis were 1) Atrophy of the hair follicles, 2) Atrophy or thickening of the epidermis and hyperpigmentation, 3) Gradual ulceration involving the subcutaneous tissues.

FORSSELL describes KIENBÖCK and SCHOLZ' and HEINEKE's experiments with the total irradiation of mice and rabbits in which a number died without any visible tissue changes, of course that is to say, without epilation. One therefore presumed »a direct effect upon the central nervous system or a general disturbance of function similar to the one caused on the skin». FORSSELL pointed out that it might be that a blood change could be the cause and suggested systematic blood counts.

He finally refers to BECKET's experiment (1903) of the simultaneous irradiation of a small epithelioma, a wart, and healthy skin. The epithelioma commenced to atrophy at the end of three days, the wart after a week but the healthy skin first showed signs of reaction at the end of fourteen days; this showed the higher degree of radio-sensitivity of the more differentiated tissue.

He suggested that the primary indications for roentgen therapy were in diseases in which epilation was the chief aim (favus, sycosis), then in diseases of the skin such as eczema, prurigo and tuberculoids, and last in skin tumours. He gave an account of the first case of cancer of the skin cured by means of roentgen treatment (STENBECK 1900). He concludes with the sentence »only superficially growing skin cancers can be permanently eradicated by means of roentgen light». He seems to concur with VON BERGMAN's view (1903) »that all cancroids must be radically excised by operation».

Finally, FORSSELL pointed out that doctors »must consider protecting themselves against the roentgen light and a surgeon must be especially

careful of roentgen dermatitis of the hands». ALBERS-SCHÖNBERG had in 1903 recommended »protection around the lamp» and a lead cubicle for the operating doctor.

This work shows with what thoroughness FORSSELL prepared himself for his coming activities. It contains seventy-eight literary references.

FORSSELL's next work in radiotherapy deals with *cancer of the skin and the lip*. Already in 1909 he described eighteen cases of infiltrating cancer of the skin which he himself had treated with large doses over a short time-period. The so-called *primitive method* of small daily doses with a long time-period (compare STENBECK's first case of cured superficial cancer of the skin page 423) had previously been used. FORSSELL now stated that with the increased possibility of obtaining precise dosage, treatment by means of large doses within a short interval of time (the so-called *expeditious method*) should be employed. The treatment was carried out with a beam of unfiltered radiation, the neighbouring regions being well protected, with a distance of 16 cm and a dosage of 10 to 12 *H* spread over two sessions. The published illustrations of cures depict quite nice pale scars in the skin substance.

FORSSELL indicates that the scientific basis for radiotherapy is already laid, that its indications commence to take more concrete form but that much work still remains for perfection of technique and for an improvement in the method of dosage.

In 1917, FORSSELL published twenty-four cases of cured carcinoma of the lip. These cases had been treated with tubes of radium encased in plastic moulds, a method described in some detail by EDLING and BERVEN. FORSSELL shows here several well-advanced cases of cancer of the lower lip and points out the selective degenerative action upon the tumour cells and which results in reabsorption almost without trace and a plastic cure without blemish even in the case of wide-spread tumours.

He laid down the following indications 1) Radium treatment alone in the case of superficial as well as for infiltrating growths without obvious gland metastases, 2) Glands should not be removed prophylactically if they are not the site of metastases, 3) If metastases be present in the glands, they should receive pre-operative irradiation and afterwards a block resection should be carried out. Excellent palliative results and even freedom from physical signs can be obtained in the case of inoperable primary tumours and inoperable metastases.

FORSSELL has made particularly valuable contribution to the *treatment of the female genital organs*. His first communication upon the radium treatment of advanced inoperable tumours of these organs appeared in 1912 in the form of an address »*Radium treatment of malignant tumours in the female genital organs*» given to the Swedish Medical Association. He here showed how more than half the patients with high

degrees of anaemia and lowered general condition after protracted bleeding and with offensive discharges and severe pain, were appreciably improved and in about ten per cent of cases became clinically free from signs with a complete disappearance of the palpable tumour. Two cases of cancer of the ovaries had been similarly treated; one became free of physical signs and the other considerably improved. The treatment consisted of a local radium application lasting from 18 to 24 hours upon two or three occasions, of 100 mg of radium element filtered with 2 mm of lead, that is to say the »Stockholm method» *in nuce*.

These results attracted very great attention and led thereafter to the Swedish gynaecologists sending even border-line cases and in solitary instances, operable cases to Radiumhemmet.

In 1914, in a longer essay, FORSSELL gave a more detailed account of the method of treatment in use at that time. As regards technique, he now prescribed treatment with greater filtration, *i. e.* 2—4 mm lead filters, and advised the introduction of a tube of radium into the cervix. He called attention to the necessity for adequate secondary filtration, subjects general and local reactions to careful analysis, and discusses injuries and their causes in detail.

In his final sentences, FORSSELL says that in spite of the purely local effect of radium treatment, it produces an important improvement even in inoperable cases and in about ten per cent of cases, freedom from signs. He suggests that no other form of treatment of these inoperable cases can show a comparable result. He further suggests that it is possible that operable cases of carcinoma of the cervix will as a principle come to be treated radiologically and not surgically. He states, however, that the radium treatment of operable cases is justified in those forms and types of cancer in which the treatment of inoperable cases gives promising results.

Experience regarding the permanence of the primary cures obtained was still too small and the observation time too short for one to be able to decide definitely in favour of the radium treatment of operable cases.

After 1914, the treatment of cancer of the uterus was taken over by JAMES HEYMAN who developed FORSSELL's inaugural methods still further. HEYMAN's great work of the year 1918 on carcinoma of the cervix, principally based upon FORSSELL's material stressed the permanency of the primary freedom from physical signs obtained by ray therapy. The most important result of this treatment was that Sweden's leading gynaecologists concurred with FORSSELL's and HEYMAN's conception of the superiority of ray therapy to surgical treatment. From that time onwards the operative treatment of carcinoma of the cervix has practically never been carried out in Sweden. FORSSELL's pioneer work in that field has thus born rich fruits.

Quite one of FORSSELL's most outstanding achievements in the sphere of ray therapy is his work »*On the permanency of radiological healing in malignant tumours*». FORSSELL has published several works on this subject during the years 1924 to 1933 and also raises these questions in many of his lesser works upon growths. Surgeons and radiotherapeutists were — then as now — in disagreement by reason of the fact that surgeons generally doubted the possibility of permanently curing malignant tumours by irradiation.

FORSSELL calls attention to the fundamental difference between a surgical cure and one effected by irradiation. The surgical method removes mechanically and as radically as possible the tissues which are clinically infiltrated, and ordinary healing of the damaged tissues afterwards occurs. Permanent healing can only be attained if the tumour be completely removed and should this not be the case, recurrence inevitably takes place.

By radiotherapy, on the other hand, the malignant tissue throughout the whole of the area irradiated is dealt with, an area much more extensive than one that can be removed surgically. Under the influence of the radiation the tumour itself — without outside intervention — begins to regress and finally disappears more or less completely. Healing generally takes place through gradual resorption, attended by a cleaning up of the ulceration, cessation of bleeding and a final rebuilding of tissue which will differ very little or not at all from the normal. Surgical interference produces healing in a wound following extirpation of the morbid tissues. Radiotherapeutic healing eliminates the morbid growth through the action of the healing process itself.

FORSSELL also has the definite conviction that the irradiation of a tumour produces other than a local effect. From his experience the local healing process causes the whole organism to become more resistant to tumour diseases in general. The local reparative processes cause the formation of certain anticancerous elements and these by their presence help to increase the power of the human body to resist the disease. The possibility of an increased general resistancy seems in consequence to call for the adoption of pre-operative radiation treatment carried out as effectively as possible.

After FORSSELL had propounded these fundamental differences between surgery and ray therapy he stated that it was difficult at that time to make a reliable comparison between the permanent cures effected by surgical and radiological treatment. There were certainly numerous reports of primary healing but more extensive material was required in order to make a more effective comparison of the permanency of such cures. It is only in the case of growths situated in the skin, buccal cavity and on the lips, in cancer of the cervix, and in certain sarcomata that it

is possible to make such a comparison. There fortunately exists from that period a publication with cases exclusively surgically treated: namely NYSTRÖM's *Cancer diseases in Sweden*, Stockholm 1922. FORSSELL now compares the results of surgical treatment alone and of pure radiological treatment. The figures for cures in the radiological material are based upon cases from Radiumhemmet up to 1919. He reports in cancer of the skin a five years cure in 78 % of cases treated with radiotherapy as against 63 % with surgery: in cancer of the lip 86 % and 73 % respectively; in cancer of the mouth 53 % and 41 % respectively; and in cancer of the cervix (operable and border-line cases) 40 % and 36 %.

In all these situations taken together he consequently makes a comparison in favour of the cases treated radiologically.

FORSSELL afterwards investigates the frequence of recurrence after primary cure. Local recurrences appear in the main in the first and second year after treatment. Recurrences occur in skin cancer after radiological treatment in 20 % of cases — after surgical treatment in 24 %; the figures for superficial cancer of the lip are 13 % and 27 % respectively; for infiltrating cancer of the lip 17 % and 38 %; and in cancer of the uterus (operable and border-line cases) 31 % and 47 %. When primary healing has once been secured by radiotherapy, the percentage of recurrences is lower than after primary surgical healing.

In the investigation of results in certain forms of sarcoma, FORSSELL states that the cures by radiotherapy are obviously superior to those of surgery in the case of quickly growing radio-sensitive tumours, especially in reticular cell sarcomata. In discussing the outer appearances of these sarcomas he uses the winged words: »Those highly sensitive rapidly growing tumours seem to cry out to the knife: Do not touch me!»

Upon the basis of the material collected, FORSSELL is of the opinion that he has shown that cures resulting from radiological treatment of operable tumours in the situations mentioned above are comparable with or superior to those arising from surgical treatment alone.

In cases where metastases have already occurred, combined radiological and surgical treatment must, however, according to FORSSELL's conception, be carried out. In this connection he points out, for the reasons mentioned above, the necessity for a thorough pre-operative treatment by irradiation.

FORSSELL then seeks the reasons for the many poor results obtained in different clinics by ray therapy. He finds that they are caused by lack of control, insufficient experience and inadequate resources and shows that radiotherapy must be centralised in special well-equipped clinics with specially trained doctors working in large laboratories (radiophysical, radiopathological, and research laboratories) and who »devote life and soul» to their work. He indicates the necessity for the radio-

therapeutic institutions to lie in direct association with large hospitals and for the existence of an intimate co-operation between the special departments of the hospital — surgical, gynaecological and otological.

In the »Nordisk Text-book of Surgery» (1932), FORSSELL gives an excellent description of the biological effects of roentgen irradiation. He differentiates on the one hand between primary damage caused by irradiation and on the other hand inflammatory changes, both of which biological processes become closely interwoven during the reaction time.

Injuries due to irradiation consist of the immediate physical effects — changes in the electrical charge upon the atom — and biological changes which first appear after a certain latent period.

The actinogenous inflammatory reaction takes place in the tumour bed and is to be regarded as a curative reaction of the tissues against the damage caused by the rays. It runs its course like any other process of inflammation, that is to say there is redness, swelling, heat, pain and *functio laesa*. This cell and tissue reaction develops in three phases: 1) Irradiation injuries to the cells, 2) Cell and tissue destruction produced by the activity of the inflammation of the tissues and 3) The breaking down and involution of the inflamed tissue. These inflammatory processes lead to a cure.

These reactive changes are of the greatest importance in the healing processes affecting malignant tumours. If the tissues for one reason or another be injured so that an inflammatory reaction cannot take place, as for example, in tissues with poor nutrition and poor powers of reabsorption (in tissues with existing permanent injuries of their vessels, in thin tumour beds &c.), it will be difficult to obtain a permanent cure. The importance of the rôle of the reactive inflammation in affecting a cure in ray therapy has led FORSSELL to form again the opinion that pre-operative irradiation treatment should be carried out in all cases.

In different papers FORSSELL has described the technique and given the indications for the treatment of *laryngeal* and *pharyngeal cancer* and of some *sarcomas*.

He is of the decided opinion, that the pre-operative treatment plays an important rôle in the permanency of the healing of breast cancer (»*The pre-operative treatment of breast cancer*» and »*Combined surgical and radiological treatment of breast cancer*» — both published in Swedish in Nordisk Medicin, Stockholm, 1940 and 1941).

In three publications he gives his experiences of *roentgen therapy in medical diseases*. He emphasizes the good effect of roentgen treatment of Graves' disease: »*The experiences of the roentgen treatment of Morbus Basedowi*» — with O. SANDSTRÖM — (Proceedings of the Northern Surgical Society, Gothenburg 1927). He obtained freedom from signs and

symptoms and full capacity for work in 53 % and full capacity for work but with persisting slight signs of exophthalmus in 23 %, about the same curative effect as with surgical treatment at that time.

Electrotherapy

In the Spring of 1908, FORSSELL took the opportunity of studying at Keating-Hart's in Marseille the method, which the latter had demonstrated in the year 1906, of influencing diseased tissue by means of high-frequency electrical currents. The attack should be of a two-fold nature, and consist partially of a pure destructive process and partially in the production of a reactive process of defence in the surrounding tissues.

It was generally thought at this time that roentgen treatment could only cure very small and superficial skin cancers and that a radical operation was the only possible means of affecting a cure in the cases of deep-seated cancers. FORSSELL was able to see and examine several deep-seated cancers of the face during the course of his visit: they had been treated by the Keating-Hart method and presented neat scars.

Upon his return home, FORSSELL described the method in an address, »*On fulguration and roentgen treatment of carcinoma of the skin*» given to the Swedish Medical Association and expressed the opinion that it seemed to be of promise in the treatment of infiltrating growths.

He afterwards proved the method, however, himself and already by the end of the year his mind was made up. He stated that fulguration has only a destructive and no selective action upon tumour tissues. He did not hesitate in the choice between roentgen treatment and fulguration.

Statistics

During the earlier years of Radiumhemmet's activities, FORSSELL was energetically engaged in working upon the whole of the growth material. He has made a collective »*Review of the results of the treatments of growths at Radiumhemmet 1910—1911*» and again »*1910—1915*» which were published in the Scandinavian journals. FORSSELL considered, however, that such information concerning the results of treatment, ought to be given out yearly. His essays on the need for a permanent organization for the control of treatment led to the inauguration of the »follow-up» department in Radiumhemmet through the medium of which the control of results in all cases became possible. A statistical report is now published each year by Radiumhemmet in the Cancer Association's annual report.

The Organizing of the Fight against Cancer

A very great part of FORSSELL's work consisted in the organizing of the fight against cancer. It was in the year 1910 that Radiumhemmet was first founded in Stockholm through the initiative of private individuals: trial treatments of malignant tumours were to be undertaken with radium and roentgen rays.

When King Gustaf V celebrated his seventieth birthday, the Swedish people collected five million Crowns, which the King donated for the combat against and for the investigation of cancer. King Gustaf V's Jubilee Fund, the Cancer Association, the Swedish Government and several municipalities then founded the three Jubilee clinics in Sweden — in Stockholm, Lund and Göteborg — together with their research departments.

FORSSELL was one of the leading figures and the promoter by speech and in writing both in the collection of the subscriptions and the drawing up of the plans for the Jubilee Clinics. In nine different works he points out the necessity for the centralization of all radiotherapy in large central well-equipped clinical departments. To these departments must be attached further departments for radiophysics, radiopathology and general research into growths, and for statistics. The radiological hospital must be placed in direct connection with a large clinical hospital so that an intimate co-operation with the staff, above all with the surgeons, gynaecologists and otologists, may be reached.

FORSSELL's work resulted in an organization which now functions very satisfactorily. Radiology is represented in the Universities of Sweden by seven professors, four in roentgen diagnosis, one in radiotherapy, one in radiophysics and one in radiopathology. Moreover there are six associate professors in radiotherapy, one associate professor in cancer research and one in radiopathology.

Since the time that this organization in Sweden has been completed and proven, FORSSELL has published fifteen different works in English, French and German, in which he gives an account of the fight against cancer in Sweden and of the results obtained in this campaign.

FORSSELL's exceptional services in this domain consist in the fact that he has, through his effort, brought medical radiology up to the status of an independent science and an independent teaching subject on the same par as the other branches of medical science. This, his work, has not merely born rich fruits for Swedish radiology but has influenced and stimulated development in other countries, above all in Denmark, Finland and Norway.

Teaching

FORSSELL was interested to a high degree in the teaching of medical radiology. He considered that every doctor should have a basic and comprehensive course in the subject at an early stage of his medical career followed by a special course after the main subjects — medicine, surgery and gynaecology — had been studied.

He has published a number of works in the field of teaching. An account of these appears in the obituary (page 427). FORSSELL was of the definite opinion of the necessity of dividing the large subject of radiology which was altogether too vast for one man to master. This division in diagnostic and therapeutic radiology is, according to FORSSELL, of the very greatest importance not only for practical working and research but for teaching.

FORSSELL expressed his interest for teaching and for the bringing up of youth when he accepted the post of »inspector» of his old school. In this position he exercised for many years an important influence upon the rearing of young people. Orations which he delivered upon commemoration days to the assembled youth were expressions of his conceptions of life and gave the listeners significant instruction regarding its problems. Parts of these speeches are published in various journals and appear in the bibliography.

Finally, FORSSELL has carried out an investigation as to what extent scholars with good school reports, the so-called »bright sparks» maintain their positions afterwards: *»Observations on the study results in medical students»*, Stockholm 1938. FORSSELL has come to the conclusion that students with good school reports acquitted themselves particularly well during their medical curriculum, and drew the inference that scholarships and study grants could well be awarded with the school reports as guides. Scholarships then always appear to reach the right hands.

Hospital Construction and Organization

As was pointed out earlier, FORSSELL was an exceptional organizer. His comprehensive organizing activities encroached unfortunately much too much upon his scientific work. He says himself: »My scientific works have in the main taken shape in the silent shades of night.» We Swedes must, however, consider ourselves fortunate that he devoted so much time to the work of organizing.

I have already mentioned his organizing of medical radiology into an independent field of research. It was mainly through his resolute energy that the two great University Hospitals, the Karolinska and Sabbatsberg Hospitals, came into existence. By speech and prose in

official statements he put forward his ideas and fought for their execution. He thus published sixteen exhaustive works and nine detailed statements in this field. The first lines of these works commence with a description of his early roentgen institute at the Serafimer Hospital in 1913 and end in 1949 with a presentation of the very important proposal that Stockholm's City Hospital, Sabbatsberg, should be opened for medical teaching.

Biographies and Bibliographies

During his long spell as editor of Acta Radiologica, FORSSELL wrote over thirty biographies — among others, those of ALBERS-SCHÖNBERG, BERGONIÉ, CARMAN, KNOX, HAUDEK, HOLZKNECHT, RIEDER and MARIE CURIE and produced the four bibliographies of LAURELL, HEYMAN, CLAESSEN and FORSSELL. He was personally acquainted with and on good terms of friendship with the men whose pictures he drew. He possessed an outstanding knowledge of their scientific works and of their practical activities. This part of FORSSELL's works gives a valuable and extremely interesting insight into the history of radiology during the last thirty years.

Life Assurance

FORSSELL was for several years consultant to one of Sweden's largest life assurance companies after his retirement from the professorship; he became interested in this work. He has written two essays during the period on the risks entailed in the life assurance business.

Elis Berven

THE ROENTGEN DIAGNOSIS WORKS OF GÖSTA FORSSELL

Words of remembrance at the meeting of the Swedish Medical Association, Nov. 21st 1950

The task has been given me of rendering a survey of the scientific works of GÖSTA FORSSELL as far as they concern the field of roentgen diagnosis.

In going through GÖSTA FORSSELL's bibliography of some two hundred works, covering half a century from 1899 to 1949, one gets a feeling of the very deepest admiration and warm gratitude mixed with a sense of melancholy. This bibliography, published in October 1949, together with the voluminous and representative collection of individual items, bound in three huge volumes, was shortly afterwards presented by the author to twenty libraries in this country including that of the Roentgendiagnostic Department of the Karolinska Sjukhuset.

The roentgen diagnostic section of GÖSTA FORSSELL's works is, it is true, only about half as large as the two volumes devoted to radiotherapy and radiological organization but on the other hand its contents are particularly comprehensive. It presents a review of the enormous development of roentgen diagnosis during that important early period and consists of a great cavalcade of memories, contributions, controversies, discussions and problems of those days the solution of which was demanded from routine roentgen diagnosis.

The diagnostic material can be divided into two main groups, one embracing the works on roentgen anatomy and roentgen physiology and the other those on clinical roentgen diagnosis and technique. FORSSELL's first roentgenological investigation consisted of a *roentgen examination of the movements of the wrist in human subjects*. This was published in the *Skand. Arch. f. Physiol.* in 1901 and was inspired by FORSSELL's intimate co-operation with Prof. ERIK MÜLLER at the Institute of Anatomy. It was worked out during FORSSELL's first roentgen post as assistant at Dr. T. STENBECK's private Roentgen Institute in Stockholm: this incidentally was accommodated on the ground floor of what is now no. 63, Mäster-

samuelsgatan. The premises, now used as a shop, still remain to this day. FORSSELL worked under primitive conditions without direct daylight on a kind of built-up intermediate floor at the back of the little room. By careful detailed analysis of a great number of roentgenograms taken in different positions of the wrist-joint and by comparing them carefully with anatomical specimens, FORSSELL demonstrated for the first time in this work on living material, the complicated mechanism of movement and the relative changes in position of the small bones of the wrist-joint.

In two following earlier works from the Serafimer Hospital FORSSELL deals with the *roentgen anatomy of the bony pelvis* with special consideration of the various calcifications in vessels which may cause *errors in the diagnosis of urinary stones*. They were comprehensive and fundamental roentgen anatomical works for those times and were based upon progressive dissections of various layers of the pelvis in combination with repeated roentgen control examinations of the material. The course of the ureters and the situation of the ureteric orifices were indicated by bronze-aluminium wires placed in situ. As a foundation upon which the differential diagnosis could be based, important calcium-dense shadows in the pelvis were dissected out, localised, and their nature determined. These included calcifications of the arterial walls and phleboliths, prostatic calcifications, calcifications in tuberculosis of the mucous membrane of the bladder, calcifications in the region of the sacrum in a blocked tuberculous ureter and finally stones in a completely occluded diverticulum of the bladder. It is a classic work on the differential diagnosis of concrements in the urinary tract in the pelvic region at a time when the advantages of the routine use of contrast media for outlining the urinary passages were unknown.

Rudimentary ribs on one or both sides of the two upper lumbar vertebrae were observed by FORSSELL in 3 to 4 per cent of the cases and reported (1908) as important in the differential diagnosis of fractures of the transverse processes in these regions.

It was the alimentary tract and especially *the stomach and its movements* which soon completely absorbed FORSSELL's interests in the fields of roentgen anatomy and roentgen physiology. It was in this field that he afterwards wrote his great thesis for his degree (1913) following shorter communications. FORSSELL's living interest for these regions was inspired by his teacher, intimate friend, and professor in anatomy, ERIK MÜLLER. The difficulty of obtaining conformity between the appearances noted during the roentgen examination and the anatomical descriptions of those days of the human stomach, first prompted FORSSELL to make a careful analysis of them by observing what sort of movements of the stomach and its contents were taking place during the roentgen examination. In

this way he obtained a clear picture of the essential and characteristic features of the stomach's anatomical muscular structure. These roentgen examinations were primarily carried out in order to study the connection between the mechanism of movement in the human stomach and its anatomical structure. They caused FORSSELL to make an exhaustive and purely anatomical study, among other things, of the muscle structure of the stomach wall. On anatomical specimens fixed and coloured in various ways, he dissected and analysed their muscle structure better, more carefully and thoroughly than had been done up to that time. He supplemented this with comparative anatomical studies of the stomachs of different kinds of animals. This most careful and time-taking investigation led to the foundation of a new and better *nomenclature* for the segments of the human stomach. This nomenclature was directly based upon the variations in the muscle structure in the different parts of the stomach and is now used in most parts of the world. It has supplanted the unsuitable and often quite erroneous designations previously in use. FORSSELL pointed out that each section of the stomach has an absolute constant anatomical structure, its own typical muscle architecture, directly causing the characteristic forms and contractions within the various segments which appear on the roentgenograms.

FORSSELL pointed out that a constant and typical arrangement of the muscle fibres in relationship to the existing supporting and strengthening structure was the guiding principle in the architecture of the musculature of the stomach.

The fundamental shape of stomach construction always persists even in shapes which may vary functionally. With a knowledge of the laws affecting the scheme of movements in the walls of the stomach, one can deduce functional variations in shape directly from the muscle structure. Behind the variations in shape, taking place according to these laws, there lies a unity of structural continuity of the stomach wall. The constant muscle structure is directly reflected during the variations in form and movements of the stomach.

FORSSELL's works covering *the connection between the movements and the muscle structure of the stomach* amount to twelve numbers and kept him busy during three complete decades (1910—1940). Included in this section is his contribution on *The question of gastroptosis*, as well as *The use of bandages for gastroptosis*, *The relationship between the shape of the thorax and the shape and position of the stomach*, his works on the so-called *Pathogenesis of pyloric spasm* and *Congenital pyloric stenosis* and on *The function of gastro-enterostomy and the most suitable location for the anastomosis in the surgical treatment of gastric and duodenal ulcers*. In the latter work, FORSSELL called attention to the fact that the conditions under which the stomach emptied in gastro-enterostomy depended

both upon the site of the stoma in relation to the different segments of the stomach structure and also upon bodily posture. FORSSELL pointed out that the physiological site of election was next to the major curvature in the distal part of the sinus ventriculi close to the canalis ventriculi. The emptying rate of the stomach, controlled radiologically, can be modified within certain limits by suitable posture during the actual meal and shortly afterwards.

Concerning the conception of gastroptosis, FORSSELL observed that a low position of the stomach with the patient erect permitted no conclusions whatever regarding its pathology. It is a normal function of the stomach, by changing its vertical length, to follow the varying height of the supporting basis.

A question which occupied FORSSELL to a still higher degree during nearly all his professional life, and which he also considered was his most important scientific discovery, was the one concerning *the mechanical fine division of the ingested food by the independent movements of the mucous membrane of the digestive tract*. This theme is dealt with in a total of twenty-four different works in FORSSELL's bibliography covering the years between 1913 and 1941, for the first time in the form of a special chapter in his previously mentioned doctor's thesis (1913).

FORSSELL here showed that the mucous membrane of the stomach by an inherent reflex mechanism in its own musculature (*muscularis mucosae*) could alter the size of the stomach's lumen independently of the state of contraction of the muscles in its walls (*tunica muscularis*). The independent mechanism of contraction of the mucous membrane is complementary to and a refinement of the muscular canal's own rough mechanical division of its contents. The whole process of digestion is thereby assisted. The pattern of the mucous membrane relief can cause significant deviations between the roentgenological appearances of the filled lumen and outer contours of the stomach walls. And this is especially true in a condition of marked contraction of the stomach or its particular segments. Some of these deviations appear partly as local defects in the silhouette of the stomach and others as generalised folded, bulky transformations in the contour.

The rôle of the mucous membrane was formerly considered to be concerned purely with bio-chemical functions, *i. e.* digestive processes and re-absorption. The folds of the mucosa were perceived either as fixed anatomical entities or resultant from a passive gathering up of the membrane as a direct result of contractions in the surrounding muscle tube.

FORSSELL has shown that the mucous membrane has the power, previously unknown, to model and arrange its folds on its own, and quite independently of the contraction of the outer tube of muscle, in other

words, an inherent motor function, a, what FORSSELL called, »*Autoplastik*». He succeeded, as a matter of fact, in demonstrating by means of anatomical specimens hardened in situ that the mucous relief pattern and the size of the lumen could vary within wide limits even when the size of the muscle tube remained unaltered. Roentgen examinations of living subjects after the administration of opaque media confirmed these findings. The mucous relief pattern in one and the same place could change in appearance from one moment to another in spite of the absence of any alteration in the size of the lumen embraced by the muscle tube. FORSSELL's investigation has furnished proof that the *autoplastik* of the mucous membrane depends upon the contraction of its own musculature, the muscularis mucosae. Microscopic examinations have shown that this musculature is thickened upon the crest of every fold by a piling up of the fibres. It has also been shown in the same way that the vessels in the mucosa assist in the formation of the folds: both the blood capillaries and the lymph vessels are widened in the region of the folds but are relatively contracted in the region of the grooves between them.

The breaking up of the food substances into relatively large particles is brought about by the action of the tunica muscularis of the digestive canal. The finer control and the more intimate division of the particles is brought about by the varying folds of the mucosa: the folds will sometimes work against and at other times assist the contractions of the muscle wall. As regards function, the types of folds found in the mucosal pattern may be divided into two main forms, the rest or empty form and the active form. FORSSELL differentiated between several different types of contraction associated with blocking or filtering devices, smooth or corrugated transporting tubes, digestive chambers and re-absorption reservoirs.

This FORSSELL's epoch-making discovery of the independent powers of movement inherent in the mucous membrane of the alimentary tract has been of the greatest significance in roentgen diagnosis. It has enabled us to understand more clearly the changing formation of the mucous membrane and to interpret the variable pictures of pattern which are seen during the different phases of the process of digestion. Many conditions of disease, such as ulceration, tumour formation and inflammatory changes cause typical alterations in the form and the movements of the mucosa. Several functional changes are also associated with distinctive alterations in the *autoplastik* of the mucous membrane. The whole of the modern conception of the diagnosis of changes in the mucous membrane of the alimentary tract are based essentially upon an appreciation of the *autoplastik*.

We have thus been given an insight into the manner in which food substances are broken down into fine particles during the process of

digestion. We are able to understand that the digestion and progress of the ingesta in the various parts of the alimentary tract, *i. e.* the stomach, small and large intestines, does not only occur by mass peristaltic movements of the musculature, but also by their carefully regulated and fine selection in small, sometimes very small, quantities.

The *autoplastik* of the mucous membrane regulates the mechanical fine division of substances during their passage through the various parts of the digestive canal with precision and in an extraordinarily many-sided and effective manner. The *autoplastik* can from one moment to the next change any part of the pattern of the mucosa. It is thus enabled to fit in best with the changing needs of digestion, food absorption, storage and transport. At one moment it may be occupied with one task, and in the next with another.

FORSSELL, unfortunately, never got the opportunity as he so earnestly desired of dealing in detail in one large monograph with his gigantic collection of material on the *autoplastik* of the mucosa in normal and pathological changes, in functional and organic disturbances. This must be regretted for it would certainly have led to a deeper appreciation of the essential character of the processes of digestion.

FORSSELL's works in the realm of pure clinical roentgen diagnosis amount to sixteen, and touch upon the most varying spheres of roentgen pathology: some of them consist of relatively short communications together with observations made during the course of the discussions. They include the following: *The significance of the radiological examination in the diagnosis and treatment of stones in the bladder. Pathological irritation of ossification as a roentgen sign of fungus disease in young subjects. Köhler's disease of the os naviculare pedis. The anatomical basis of the ulcer niche. A contribution to the roentgenological diagnosis of ulcus pepticum-jejuni. The significance of the roentgen examination in the early treatment of gunshot wounds during war. The roentgen anatomy of the lungs, with special reference to the hilar shadows*, and *The roentgen diagnosis and differential diagnosis of carcinoma of the colon.*

Other works of a pure roentgen diagnostic nature are of greater size. In collaboration with C. D. JOSEPHSON, FORSSELL rendered a detailed essay on *The roentgen diagnosis in tuberculosis of the kidney* in the Jubilee volume of Hygiea in 1908. The roentgen diagnostic technique of those days in the examination of the kidneys and the use of the Albers-Schönberg compression diaphragm as an aid in showing the kidney outlines, was discussed most thoroughly. The authors described in detail such cases where the roentgen examination had materially assisted in establishing the diagnosis. In one case it was erroneously believed from the clinical examination that the patient had only one kidney. The roentgenological examination showed, however, an obviously dense renal shadow on the

doubtful side: parts of this shadow presented changes of a »putty» nature — that is to say — a number of cavities of various sizes filled with inspissated material of a calcareous character. Operation completely verified the roentgen diagnosis of a condition of »putty-kidney». The kidney was removed but the patient gradually became worse and died by reason of a tuberculous infection of the other kidney which, however, had not shown any characteristic calcifications in the parenchyma or deformity of outline in the roentgenograms. In another case of unilateral renal tuberculosis, the roentgen examination demonstrated the shadow of a kidney upon the unaffected side. This other kidney was thought to be absent and consequently the patient was spared a proposed exploratory incision. In our days of modern urography, the cases would naturally have been investigated in a simple and innocuous manner; the cases, however, show us clearly the diagnostic difficulties of those times.

The radiology of endogenous prostatic stones was sketched in three essays (1908—09) on the basis of an anatomical investigation in this field. Prostatic stones are described as being, as a rule, bilateral, generally arranged in two relatively symmetrical and characteristic groups on each side of the mid-line, two to three centimetres behind the symphysis pubis, although sometimes in conglomerations. They are generally markedly dense, sharply outlined and consist in the main of calcium phosphate. He observed that the differential diagnosis of tuberculous calcifications in the prostate and the seminal vesicles should always be born in mind but that the diagnosis, by reason of the typical appearance and situation of the opacities, was usually easy.

Forssell devoted five different essays (1909—20) to the *Roentgen diagnosis of tuberculosis of the bone system*. Typical roentgen findings in tuberculous foci in various regions of the bony skeleton at different ages were adequately and beautifully illustrated by material gathered from cases of tuberculosis of the joints and bones confirmed clinically. In a number of cases, the differential diagnosis in interesting affections of the bony skeleton was pointed out, and mention was made of the value as well as of the limitations of roentgen diagnosis.

In 1916, in collaboration with Einar Key, Forssell described with great care *the first case of a diverticulum diagnosed roentgenologically in the second part of the duodenum*. It was also the first case of a duodenal diverticulum so discovered that had been treated radically. The characteristic roentgen signs consisted of the presence of a rounded, somewhat mobile, extra-duodenal deposit of the contrast medium lying in the region of the second part of the duodenum, and persisting for four days. According to the author's opinion, the demonstration of such a diverticulum should as a rule be the indication for surgical interference.

FORSSELL gave an address to the Svenska Läkaresällskapet (*Swedish Medical Association*) in 1918 on the *Roentgen diagnosis of appendicular changes in chronic appendicitis*, afterwards published in the Proceedings of the Association. In the address, which was followed by the demonstration of a beautiful series of roentgenograms, it was suggested that the commonest radiological signs in disease of the appendix, were changes in the form and size of the lumen, irregular contrast filling persisting throughout the various examinations, and a fixation of the appendix as noted by manual palpation. Other signs which might be observed were a localised tenderness upon palpation confined to the appendix itself in cases where the appendix was mobile, and finally a retention of the contents when the caecum was empty. This last sign also seemed as it might indicate a quiescent appendix in which the musculature was weakened and in which there was a likelihood of a recurrence of the inflammatory process. Non-filling of the appendix did not, in itself, seem to signify any conclusive pathological change. In spite of the fact that radiological examinations still played a relatively modest part in the diagnosis of appendicitis, it was the author's opinion that with increased knowledge they could become a valuable source of help in the solution of doubtful cases; an opinion that is still prevalent, if the patient is carefully prepared with a thorough evacuation of the bowels.

FORSSELL has on several occasions dealt with questions affecting *diagnostic technique* especially in his works on roentgen diagnosis covering the first decade. Thus, in two articles he dealt very thoroughly with the *technical improvements* he had introduced *on Holtzknecht's vertical screening stand*. These consisted of a device which made it possible to take roentgenograms immediately following screening, a simpler but at the same time better method of making orthodiagrams, the introduction of a special cassette-holder to facilitate precision roentgenography, and in bringing about an effective method of compression on the screening-stand. FORSSELL also published an article on the construction of an illumination apparatus with a diaphragm and a parabolic reflector for the examination of roentgenograms with indirect artificial light, *i. e. a lightbox for the examination of pictures called the Negatoscop. The intensification of roentgen plates of poor contrast by means of uranium salts* is recommended in three different essays, *the use of the telephone and the dictaphone* as time-saving appliances in the service of roentgenology, and finally *the use of barium porcelain in tube-shields as a new protective material against roentgen rays*. It is in the nature of things that most of the technical improvements mentioned now have interest only in the sphere of the history of medicine.

And finally, in the border-line regions of roentgen diagnosis can be mentioned an account of the examination in July 1917 of the head, the fractured thigh-bone and the gunshot injured foot of King Karl XII,

appearing in a magnificent volume, *The death injuries of King Karl XII*, published by the Karolinska förbundet (Caroline Association). In spite of the fact that the memorable roentgen examinations, in which I, among others was privileged to assist, were carried out in the Riddarholms Church with a little transportable field apparatus of that period with a small effect, the result of the examinations was conspicuously noble and the quality of the picture material, surprisingly good.

I herewith conclude this summary review of the roentgen diagnostic part of GÖSTA FORSSELL's scientific works. As a general characteristic of these works I would like to add the following few words: clarity, thoroughness, objectivity, logical keenness and expressive ability. GÖSTA FORSSELL will always live in his works. His name will for ever stand as one of the very greatest and most brilliant in international clinical radiology.

Åke Åkerlund

FROM THE GENERAL DEPARTMENT OF RADIUMHEMMET (CHIEF (AT THE TIME OF THE INVESTIGATION): PROF. E. BERVEN) AND THE CANCER RESEARCH DIVISION OF RADIUMHEMMET, STOCKHOLM, SWEDEN

BASAL-CELL CARCINOMAS OF THE SKIN TREATED BY LOCAL PODOPHYLLIN APPLICATIONS[1]

A Preliminary Report

by

Lars-Gunnar Larsson

Podophyllin derived from the roots and rhizomes of the mandrake plant (*Podophyllum peltatum*) exerts pronounced arrest of mitosis both in animal and vegetable cells (SULLIVAN and KING, CORNMAN, SULLIVAN and WECHSLER). Cytotoxic changes have further been observed in tumour cells of different origin, such as transplantable sarcomas, lymphosarcomas and various carcinomas in mice (BELKIN, HARTWELL and SHEAR, MACCARDLE a. o.). The tumour-damaging effects are induced by the following isolated components: podophyllotoxin, alpha- and betapeltatin (HARTWELL and SHEAR, HARTWELL and DETTY).

Since July 1949 50 patients with superficial basal-cell carcinomas have been treated at the Radiumhemmet by means of podophyllin applications. When this work began, no previous attempts to use podophyllin in the treatment of human carcinomas had been reported. In September 1949 SULLIVAN, however, reported 15 cases with a total number of 25 skin carcinomas treated with podophyllin and he seems to be the first one, who used the drug for that purpose. At the Radiumhemmet commercial podophyllin was used either dissolved in ethyl alcohol (95 per cent) or emulgated in an ointment containing adeps lanae, paraffinum liquidum and dextran (»Emulgon», Pharmacia) or lecithin, oleum arachidis and dextran (»Solucin», Pharmacia).[2] The concentration of podophyllin was 20—25 per cent. The tumours were treated with one superficial application per day for 4—8 consecutive days. In a few cases the tumours were treated with both the alcoholic solution and the ointment at each

[1] Submitted for publication, July 29, 1950.

[2] I am greatly indebted to A.-B. Pharmacia for valuable help.

application. Biopsies were taken prior to treatment and, in some cases, also at intervals during and after it. The microscopic changes have thus been registered 1, 2, 3, 4, 5, 11, 12, 30 and 42 days after the first day of treatment.

The first clinical effect to be noticed was a moderate hyperemia during the first 24—48 hours after the first application. The epidermal covering was then sloughed off on the second or third day and in consequence superficial ulcers appeared. During the next few days the tumour areas were covered by purulent or necrotic detritus (Fig. 2). During the week following the last treatment the ulcers rapidly cleaned up and a clean granulating wound (Fig. 3) was obtained which was gradually epithelialized during the subsequent 2 weeks (Fig. 4). The reaction was much more pronounced in the tumour areas than in the adjacent normal skin during the whole period of treatment. Podophyllin ointment applied to normal skin resulted only in a slight hyperemia but no epidermal sloughing.

Cytotoxic changes analogous to those described by earlier authors on other material have been registered. The epidermal basal-cell layers revealed extensive nuclear damage with the appearance of so-called »podophyllin cells» as soon as 24 hours after the first application. A large number of arrested and abnormal mitoses were seen at this time in the carcinoma cords as well (Fig. 5). After 4 or 5 days of podophyllin treatment the earlier typical texture was lost in the basal-cell carcinoma vegetations. The regular cancer foci became split up into small foci lying in an inflammatory matrix. The single tumour cells were in general characterized by very advanced pychnosis and swollen pale-stained cytoplasm with vacuolization. In biopsies 12 days after the last treatment isolated remnants of tumour cells were seen lying in a granulation tissue richly pervaded by growing fibroblasts and phagocytes. Six weeks after treatment the pre-existing tumour areas were covered by largely normal thin epidermis.

In 30 cases with a total number of 79 basal-cell carcinomas the time of observation amounts to 3—12 months. Complete healing was obtained in 67 out of 79 lesions. Most tumours were very superficial, intraepidermal basal-cell carcinomas and in this group almost all the lesions showed complete healing. The failures usually represented thicker tumours, where sometimes small tumour remnants were seen after the treatment. In superficial intra-epidermal basal-cell carcinomas daily applications with alcoholic solution seemed sufficient. The impression was, however, that podophyllin ointment was more effective and brought the tumours to ulceration more rapidly. Of the two ointments used »Solucin» is preferable, as it is water-soluble and easily applicable even on moist, ulcerated skin areas. Recently pure chrystalline podophyllotoxin emulgated

Fig. 1.

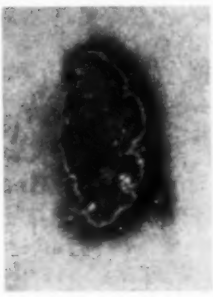

Fig. 2.

Fig. 3.

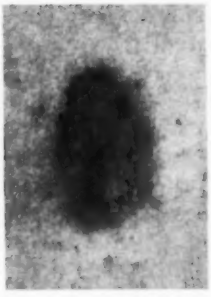

Fig. 4.

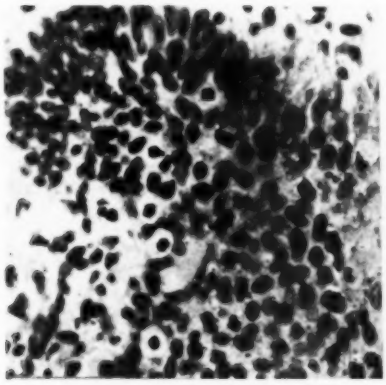

Fig. 5.

Fig. 1. Superficial basal-cell carcinoma on the trunk.

Fig. 2. After podophyllin treatment during 6 days. The tumour has ulcerated and is covered with purulent or necrotic detritus. Hyperemia in the surrounding.

Fig. 3. Two days after the last application. A clean, granulating wound is seen.

Fig. 4. Five weeks after the treatment. A reddish, smooth scar.

Fig. 5. Basal-cell carcinoma 48 hours after first podophyllin application. Several tumour cells with nuclear pychnosis and ballooned pale-stained cytoplasm are seen, probably representing early, arrested mitoses. Magn. 360 ×.

in »Solucin» was used for some basal-cell carcinomas with about the same primary reaction as podophyllin.

These results suggest that local podophyllin may be of value in the management of human basal-cell carcinomas especially for superficial, extensive or multiple lesions. A few cases of roentgen carcinomas and recurrences following previously roentgen treated basal-cell carcinomas were further treated with podophyllin applications with good primary

results. The time of observation is, however, as yet too short to justify final conclusions.

Podophyllin is a potent cutaneous sensitizer (SULLIVAN and KING). Disturbing sensitization effects, however, were noticed only in one of my patients, who got repeated treatments on large skin areas. Care should be taken to avoid podophyllin application near the eye; the conjunctive will react with pronounced chemosis. Long-time podophyllin treatment of very extensive skin areas should also be avoided until more experience has been gained.

A more detailed report including additional clinical and cytological data will be published later on.

SUMMARY

Local podophyllin treatment of superficial basal-cell carcinomas of the skin gave good primary results. The macroscopic and microscopic changes during the treatment are briefly described.

ZUSAMMENFASSUNG

Die lokale Behandlung oberflächlicher Basalzellen-Carcinome der Haut mit Podophyllin ergab gute primäre Erfolge. Die makroskopisch und mikroskopisch beobachteten Veränderungen während der Behandlung werden kurz beschrieben.

RÉSUMÉ

Le traitement local par la podophylline des cancers baso-cellulaires superficiels de la peau a donné de bons résultats immédiats. Brève description des changements macro- et microscopiques observés au cours du traitement.

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FROM THE RADIUM CENTRE IN ODENSE, DENMARK (DIRECTOR: SENIOR RADIOLOGIST PAUL JACOBY)

CANCER OF THE BREAST[1]

Results of treatment, 1929 to 1943

by

Jørgen Saugmann-Jensen and *Paul Jacoby*

Almost as long as roentgen treatment has been known the question of the importance of this form of treatment of cancer of the breast has been discussed and, in spite of the fact that it has been a burning question to all cancer therapeutists all over the world and has given rise to an enormous amount of literature, it has not yet been finally and decisively answered.

There is no lack of statistical statements of the subject, but the series of cases are too heterogeneous, and the number of treatments too few, for any safe conclusions to be drawn.

The power of roentgen treatment to reduce, in some cases transiently to cause the disappearance of, the primary tumour, is undisputed, as is also its importance in the treatment of inoperable cases.

Further, it is long-established that the pure roentgen treatment of cancer of the breast is not justifiable, and that operation is the principal treatment.

But with regard to the question as to whether roentgen treatment will be capable of improving the duration of the operative results, opinions vary much; this also applies to the discussion of the question whether roentgen treatment should be administered before or after, or both before and after the operation.

With regard to the surgical treatment, the radical operation has been the method of choice since, in 1894, HALSTED described his method. Most authors still maintain the absolute superiority of the radical operation in all operable cases, whilst during recent years a local operation has

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been advocated in early cases, in particular by English and Scandinavian authors.

The results of the Radium Centre in Odense of the years 1929 to 1943 are published in the present paper as a contribution to the discussion of the indications both of the roentgen treatment and of the surgical methods.

However, it may first be attempted to point out what may be expected in advance in such a malignant disease as mammary cancer.

Though primarily a localized disorder, confined to a small part of the breast, a general spread of the disorders will undoubtedly often have taken place before the treatment is instituted, while it will be impossible to recognize it clinically; as has been maintained, among others by ENGELBRECHT-HOLM, a dissemination may also take place *in the course* of the operation. Classifications by stages therefore become doubtful, distant metastases may have been disseminated before glandular metastases can be demonstrated clinically, and cancerous glands may also be present long before the primary tumour can be palpated.

Surgical operation and roentgen treatment can only be expected to bring about a good result as far as the primary manifestations (in the breast and the axillary lymph nodes) are concerned, whereas the patient's fate depends on the distant metastases.

The chance of recovery is, therefore, first and foremost dependent on the faculty of the organism for »neutralizing» the universal spread, of whose extent and intensity a definite view can never be formed in advance.

He who has followed for a great number of years patients suffering from cancer of the breast has a far more depressing impression than in the case of patients suffering from cancer of the uterus. Five years' freedom from recurrences does not at all mean the same in cancer of the breast as in cancer of the cervix. If a patient is free from symptoms 5 years after she has been treated for mammary cancer, one dare not for all that consider her as recovered, but will always fear the recurrence of metastases.

In preparing this statement of the results achieved at the Radium Centre it had been hoped that this impression would prove to be unfounded. It had also been hoped that it would be possible statistically to prove the superiority of the pre- and postoperative roentgen treatment, as we have gone in for this method of treatment as the main principle during the period in question. But this proved not to be the case — as will appear from the following. It is difficult to say why we have not achieved as good results with the pre- and postoperative roentgen treatment as, for example, JENS NIELSEN. It may perhaps be due to a less intense technique, which was originally decided on in order not to impair

the resistance of the patients to the cancer, and which has been constantly used in the course of the years in order not to reduce the value of the series of cases as a basis of comparison. The postoperative treatment has been administered in several series, which is primarily due to the fact that when this form of treatment was planned there were some communications which seemed to indicate that a vigorous postoperative treatment deteriorated the results—possibly by reducing the resistance of the patients to cancer. JÜNGLING's famous experiment with beans, which showed the slight sensitiveness of resting cells to rays but, in return, the cumulative effect of repeated roentgen irradiation, also seem to speak in favour of the fractional treatment.

Results of Other Authors

Radical operation only. — Although numerous statements have been published it is difficult to say what can be accomplished by operation only, partly because the results are undoubtedly greatly dependent on the thoroughness with which the operations are made, partly because the results depend on the selection of the cases for operation.

There are no statements of results of any use from this country, as both ROVSING's series of 1922 and that of DAHL-IVERSEN of 1927 had been observed for 3 years only, which must be considered too short a period.

On the basis of the literature on the subject JENS NIELSEN (1943) stated that the 5-year-result for patients who had only been operated on is about 40 per cent. There are several large, foreign statistical statements, which will not be reported here (see for instance NOHRMANN /1949/ and ANDREASSEN /1947/), but as a fair estimate of what can be achieved it can hardly be quite wrong to reckon that from 35 to 45 per cent of the patients operated on will be alive 5 years.

It must be more important to ascertain the number of patients operated on and surviving 5 years after the operation in relation to the entire series of cases of mammary cancer, in order to get an impression of how many patients recover, than is the demonstration of the number of survivors in relation to those operated on.

MC. WHIRTER states that from 35 to 45 per cent. of those operated on are alive after 5 years, with a percentage of operability of 56 (*i. e.* 56 per cent. of the entire series are considered operable). Consequently, the 5-year-result will be 45 per cent. of 56 per cent., *i. e.* about 25 per cent., at the utmost. NYSTRÖM states 40 per cent. of operable cases with 30 per cent. recovery, *i. e.* about 25 per cent. of the entire series of cases recovered. GESCHICKTER states about 33 per cent.

In order to be able to consider the supplementing roentgen treatment

to be of any value to the duration of the operative results, one must therefore require results of the combined treatment which are considerably over the 25 to 30 per cent. of surviving patients in the entire series of cases.

Radical operation + roentgen treatment. — On this subject too, numerous, partly discrepant, statements of results have been published. We shall only deal with the Scandinavian literature below, and may mention the following publications:

In Denmark JENS NIELSEN (1943) and KAAE (1947) have communicated the results from the Radium Centre in Copenhagen. Both authors clearly go in for the preoperative treatment, as they have 49 per cent. alive and free from symptoms after 5 years with this form of treatment as compared to 35 per cent. in case of postoperative treatment only.

At the Radium Centre in Aarhus GYLSTORFF-PETERSEN (1944) has stated the result of postoperative treatment to be 37.5 per cent of surviving patients after 5 years.

Both JENS NIELSEN and GYLSTORFF-PETERSEN draw attention to the fact that in the case of patients who have been operated on at a single large department (respectively the Finsen Institute and the Municipal Hospital, Aarhus) the results are better than in the case of patients operated on at the other hospitals from which the patients are sent for roentgen treatment. As far as the Aarhus series is concerned, 44 per cent. of the patients operated on at the Municipal Hospital were thus alive after 5 years as compared to only 28 per cent. of the rest of the series. In KAAE's series almost all the patients who were treated before the operation have been operated on by the same surgeon (CHIEVITZ), a fact which may have contributed to the good result of this treatment.

ANDREASSEN (1947) has communicated the results from Department C of the University Hospital in Copenhagen. However, his preoperative and postoperative series are too heterogeneous for any conclusions about the value of the two methods of treatment to be drawn from his results (30 per cent. in preoperative and 48 per cent. in postoperative treatment).

Several statements have been published from the »Radiumhemmet» in Stockholm. Lastly NOHRMANN (1949) has reported on 769 cases subjected to radical operation with preoperative, pre- and postoperative, or postoperative roentgen treatment. The percentage of survivors of the entire series was 50.6 after 5 years without any definite difference between the results of pre-postoperative and postoperative irradiation, respectively.

In, respectively pre- and postoperative, and postoperative roentgen treatment of 216 patients RÖDÉN (1944) found 52.5 per cent. and 39 per cent. alive after 5 years.

BULL ENGELSTAD (1948) has communicated the results of postoperative irradiation from the Norwegian Radium Hospital; 69 per cent. of 609 patients operated on were symptomfree for 5 years. The result obtained by means of postoperative radium treatment seems to be better (71.4 per cent. of 448 patients) than that of postoperative roentgen treatment (52.5 per cent. of 139 patients). From Finland MUSTAKALLIO (1945) reported 38 per cent. alive and free from symptoms 5 years after postoperative roentgen treatment of 79 patients.

Local operation. — Radical operation is still considered by most surgeons — as well as radiologists — to be indicated in all operable cases of mammary cancer. CHASE thus says: »... to consider that local extirpation can compare with radical operation is to set back surgery of the breast more than 80 years», and BULL ENGELSTAD states: »... there is no reason why our present irradiation and surgical methods should not be continued.»

During recent years, however, some authors have communicated as good — perhaps better — results after local operation.

Therefore, it seems to be worth considering again whether, at any rate in certain early cases, we should not desist from the radical operation with its unquestionable, often intense, psychic strain for many women, and, with as good prospects of permanent recovery, confine ourselves to the far smaller interference of mastectomy or a local extirpation.

Our series of cases is only small (page 464) but seems to corroborate for instance MC. WHIRTER's (1948) and FITZWILLIAM's (1947) results.

MC. WHIRTER mentions the good results in the first-stage cases in favour of the local operation; where there are no cancerous axillary lymph nodes it must be superfluous to remove the glands. Moreover he states that recovery is only rarely seen after removal of the metastases to the axillary lymph nodes, *i. e.* in the case of radical operation in the second stage.

MC. WHIRTER (1948) has treated 790 cases with radical operation and postoperative roentgen treatment, with 32.4 per cent. surviving after 5 years, and 459 cases with mastectomy and postoperative roentgen treatment, with 42.9 per cent. surviving after 5 years. The postoperative roentgen treatment was given in one course, »repeated courses have no place in the treatment of any form of malignant disease».

The patients treated with radical operation were dealt with in the course of the years 1935 to 1940, those subjected to local operation in 1941 to 1942. In the Yearbook of Radiology, 1949, the editor states that it can hardly be considered quite out of the question that »a shift towards more favourable cases may occur with successive chronologic periods», and that the difference in time may thus explain the better results in the patients treated with local operation — which seems to be quite analo-

gous to our findings in stating the results of radical operation of the years 1929 to 1938 and 1929 to 1943 (see page 463).

Mc. WHIRTER's series of cases is apparently non-selected, whereas MUSTAKALLIO (1945) has used local extirpation in early cases (clinical first stage). Of 23 patients treated with local operation after intense preoperative roentgen treatment 6 were followed for 5 years, 5 of these were alive and free from symptoms.

NOHRMANN's series (1949) of 43 patients is also selected, comprising 30 early cases with doubtful diagnosis and 11 partly of advanced age, partly suffering from cardiac insufficiency, and, lastly, 2 with a large, ulcerated tumour which was removed in palliative operation. After 5 years 48 per cent. were still alive. Lastly, FITZWILLIAMS (1947) has reported 93 cases, »some of which by no means fell into the scope laid down for such cases, as some had actual tumours of 2 or more inches across, many had signs of malignancy, such as attachments to the skin or had palpable glands in the axilla» — thus apparently »non-selected»; 50 per cent. were alive and free from symptoms for 5 years, 66.6 per cent. were alive.

Writers' Series

The series of cases comprises all the 548 women treated at the Radium Centre in Odense in the course of the years 1929 to 1943 inclusive. The classification of the series is shown in Table I.

Table 1

Classification of Series.

	Histological diagnosis	No histological diagnosis	Total
Radical operation	274	15	289
Local operation	37	4	41
Inoperable			123
Operable — not operated on			36
Recurrences			59
Total			548

Fifty-nine patients were referred for treatment of local recurrences or of metastases after radical operation. None of these patients had had any roentgen treatment *here* in connection with the operation and are not included in the following statements.

Radical or local operation was made in 330 out of the remaining 489 cases. Roentgen treatment only was administered in 159 cases; 123 of these were inoperable when referred, whilst 36 were operable but were not operated on for various reasons.

The percentage of operability is thus 75.

All the 489 patients have been controlled for at least 5 years, or till they died, except 2 who had not been operated on. These 2 had been subjected to preoperative roentgen treatment but were then lost sight of, and could not be traced. They have both been included in deaths of cancer.

The following includes a statement partly of the number of patients who had had no recurrences for 5 years, partly of the number of surviving patients— whether relapse had occurred or not.

The question as to whether a patient is completely free from cancer may be impossible to answer, even with such a close control as the one to which our patients have been submitted, whereas it must be permissible to consider the number of surviving patients an adequate indication of the efficacy of the treatment.

No correction has been made for patients who died of intercurrent diseases.

Dosage. — The technique of our treatment and the dosage were as follows: For preoperative treatment, 2 large tangential fields towards the thorax and the breast, including the axilla, and 2 smaller fields towards the supraclavicular region and the axilla from behind. In the 2 large fields a dose of 1,500 r per field measured in the air is administered, 4,200 r in all. This treatment produces erythema and desquamation of the skin.

The patient is operated on about a month after this treatment has been concluded.

The rule is that a postoperative treatment is given about 3 weeks after the operation when the patient has recovered, though the wound may not have healed completely. This treatment comprises the same four fields, but the dose is only 600 r in each, and is repeated after 3 months.

The purely postoperative treatment is administered in the same manner, but the patient is given three courses at intervals of 2 months between the first and the second, and 3 months between the second and the third courses.

The total dose in the combined pre- and postoperative treatment gives per thoracic field about 2,700 r measured in the air, which corresponds to a dose on the skin of from 3,500 to 3,800 r. The dose in the purely postoperative treatment is only 1,800 r in the air per field, or about 2,500 r on the skin.

Localization. — Of the 489 patients primarily referred to us 251 had a right-sided and 225 a left-sided mammary cancer, whilst 7 had a bilateral affection, and 6 cases had not been fully elucidated; *i. e.* 100 cases of right-sided cancer of the breast to 90 of left-sided affection. It may

be mentioned for comparison that CLEMMESEN states 100 cases of the right breast to 111 of the left (in 4,139 cases).

Results

The whole series: Of the 489 patients 30 per cent. were alive after 5 years (141 patients operated on, and 5 inoperable) whereas only 20 per cent. (99 patients) were without any clinical or roentgenologic evidence of cancer.

Radical operation: Radical operation was made on 289 patients. The diagnosis has been verified histologically in 274 cases, whilst no such verification was made in 15 cases. The latter comprise 10 patients who were given preoperative treatment and 5 subjected to postoperative treatment. Six out of the 10 were symptomfree for 5 years (histological examination showed no signs of cancer in any of the 6 cases, which were all clinically unquestionable), while 4 died of metastases from the cancer within 5 years. No histological examination had been made in 3 out of these 4 cases, and 1 showed no signs of cancer.

Histological examination had not been made in any of the 5 patients subjected to postoperative treatment. One of these was free from relapse for 5 years, whilst 4 had died of metastases within 5 years.

Of the 289 women subjected to radical operation 139 have been operated on at the Odense County and City Hospital according to the same method. The rest of the patients (150) have been operated on at about 15 other hospitals on Funen and surrounding islands, and in South Jutland. At Odense the normal method was pre- and postoperative roentgen treatment, and when this method has been replaced by postoperative treatment only it has been in patients in whom a tumour of the breast had been removed in local operation in the belief that it was benign. As soon as the histological diagnosis had been obtained in such cases, a radical operation was made without administering, and waiting for the effect of, preoperative roentgen treatment. A few of the other hospitals had followed the same procedure, the rest have only sent the patients to postoperative treatment.

The distribution of the cases between the Odense Hospital and »other hospitals», and with regard to pre- and postoperative, or postoperative roentgen treatment, appears from Table 2.

The series of cases from Odense comprises *all* patients referred for treatment in the surgical department or at the Radium Centre, *i. e.* it is a non-selected series, which can not be said with certainty about the rest of the series.

Age-distribution: Ten per cent. of the patients were under 40 years, 65 per cent. between 40 and 60 years and 25 per cent. over 60 years.

Table 2

Radical operation: Classification according to nature of roentgen treatment and hospital where operation was made.

	Histological diagnosis	No histological diagnosis	Total
Pre- and postoperative:			
Odense	103	4	107
Other hosp.	46	6	52
Postoperative:			
Odense	32	0	32
Other hosp.	93	5	98
Total	274	15	289

Classification by stages: Histological examination of the contents of the axilla has been made in 200 out of the 274 cases with histological diagnosis of cancer.

The first stage comprises all cases *without*, and the second stage all cases *with* histologically demonstrable metastases to axillary lymph nodes.

As the classification by stages is thus exclusively based on the histological examination, a patient who is considered as belonging to the first stage may well have metastases to supraclavicular lymph nodes, or distant metastases, and should thus actually have been considered inoperable; it has, however, been attempted as far as possible to prevent this by a preoperative roentgen examination of the lungs, the pelvis and the spinal column (*i. e.* the localizations where the metastases first appear in most cases). Table 3 shows that 52 = 47.4 per cent. of 110 patients subjected to pre- and postoperative treatment were in the first stage, whereas 40 = 44.5 per cent. of 90 who had been given postoperative treatment were in the first stage. The ratio between stages 1 and 2 is thus practically the same in the two groups.

Table 3

Classification by Stages.

	Number of cases	First stage	Second stage	Stage unknown
Pre- and postoperative	110	52 = 47.4 %	58 = 52.6 %	39
Postoperative	90	40 = 44.5 %	50 = 55.5 %	35

The state of the axillary lymph nodes has been ascertained both clinically and histologically in 169 patients.

Among 115 patients without any clinical signs of metastases to the axillary lymph nodes there were 38 with histologically demonstrable can-

cerous glands, the error being 33 per cent., whereas 17 out of 54 with clinically suspicious lymph nodes did not display any signs of cancer in the histological examination; the error was thus 31.5 per cent. Table 4 shows a comparison of this result with those of some other authors.

Table 4

Comparison between the clinical and histological examination of the axillary lymph nodes.

	Number of patients	Clinical examination	
		Percentage incorrectly classified as	
		Stage I	Stage II
Gylstorff-Petersen	281	67	12
Nohrmann	609	28	15
Nohrmann, collective statistics	2 423	44	14
Harrington	1 911	29	32
Chase	?	30	30
Writers' series	169	33	31.5

Results after 5 years: Of 159 patients subjected to pre- and postoperative treatment, 34 per cent. were alive and free from symptoms, while 35 per cent. of 130 who had been given only postoperative treatment were symptomfree.

Table 5 shows these figures as well as the total number of patients who were alive after 5 years, in the case of pre- and postoperative treatment 37 per cent., and in the case of postoperative treatment 42 per cent.

When the form of roentgen treatment administered is not considered, the results are 34 per cent. alive and free from symptoms and 40 per cent. alive after 5 years.

Table 5

Results after 5 years in patients subjected to Radical operation.

	Number of patients	Results after 5 years			
		symptomfree		alive	
		number of patients	per cent.	number of patients	per cent.
Pre- and postoperative					
Odense	107	36	34	40	37
Other hospitals	52	17	32	19	37
Total	159	53	*34*	59	*37*
Postoperative					
Odense	32	14	44	19	59
Other hospitals	98	32	33	36	37
Total	130	46	*35*	55	*42*
Total	289	99	*34*	114	*40*

Table 5 also shows the results obtained, respectively, at the Odense hospital and at »other hospitals». In contrast with the results published by KAAE and GYLSTORFF-PETERSEN, there is no unquestionable difference between the two series here, as the good postoperative result obtained at the Odense hospital is presumably due only to the fact that this small series is very selected (chiefly small, non-suspicious tumours) (cf. page 460).

Table 6 shows the results (alive and free from symptoms for 5 years) in the first and second stages. There is no difference between the results of pre- and postoperative and only postoperative treatment.

As shown by table 3, the state of the axillary lymph nodes is unknown in 74 cases, but as a statement of the results in the first and second stages together gives exactly the same result as a dealing with the entire series of cases subjected to pre- and postoperative, respectively postoperative, treatment, it must be justifiable to consider the ratio found between stage 1 and stage 2 (Table 3) as applying to the entire series.

Table 6

Results after 5 years for Stage 1 and Stage 2 in patients subjected to pre- and postoperative and only postoperative Roentgen Treatment.

		Number of patients	Symptomfree	
			number of patients	per cent.
Pre- and postoperative	stage 1	52	29	56
	stage 2	58	6	12
	total	149	48	*32*
Post-operative	stage 1	40	22	55
	stage 2	50	10	20
	total	125	45	*36*

We thought it might be of interest to see whether there are any improvements of the results in the course of this quite long period. We have therefore divided the series of cases into two groups, one comprising the period from 1929 to 1938 inclusive, the other comprising the period from 1939 to 1943 inclusive.

In the former period there are 132 patients, with 27 per cent. alive and free from symptoms, in the latter period there are 142 patients, with 41 per cent. symptomfree for 5 years.

The cause of this improvement of the results is as puzzling as are the improved results of recent years in the treatment of carcinoma of the cervix (JACOBY, 1947). In our series it is not due to any change of the

technique used in the treatment, and as far as can be seen, it has not been caused either by any change of the composition of the series.

Similar results have been found by HARRINGTON (1946) in the purely surgical treatment of cancer of the breast. For the period from 1910 to 1914 he found 39.8 per cent. surviving for 5 years, whereas the result was 59.3 per cent. for the period from 1935 to 1938.

Results after 10 years: Of 145 patients 26, or 18 per cent., were alive and free from symptoms for 10 years.

This confirms the immediate impression of frequent occurrence of late metastases. The percentage of healthy survivors has decreased from 34 after 5 years to 18 after 10 years.

Frequency of local recurrence: One of the reasons why preoperative roentgen treatment should be preferred to postoperative treatment, is that fewer local recurrences are said to occur when the patient has been treated before the operation.

JENS NIELSEN (1941) thus states that 5 per cent. get local recurrences after preoperative and 25 per cent. after postoperative treatment. KAAE found, respectively, 8 per cent. and 24 per cent. of recurrences locally, *i. e.* in the cicatrice, whilst NOHRMANN has 9.6 per cent. and 16 per cent. It seems as if this can be confirmed by our series, in which there occurred 18 local recurrences in 159 patients who had been given pre- and postoperative treatment (*i. e.* 11 per cent.) and 22 in 130 patients who had been subjected to only postoperative treatment (*i. e.* 17 per cent.).

Finally it may be mentioned as an advantage of the preoperative treatment that it has an unquestionable, primary effect which often causes a decrease, in some cases complete (temporary) disappearance, of the tumour. In a statement of the results in 43 cases of cancer mammae subjected to preoperative roentgen treatment it was thus found by JACOBY (1933) that 8 tumours had disappeared, 29 had diminished, and only 5 remained unchanged. (One patient had died of another cause before the operation.) Unfortunately, a similar examination of the present series of cases cannot be made.

Local operation: Forty-one patients had a local operation. Any systematic selection of patients for this operation has not taken place, but about 50 per cent. of the patients were over 60 years (as compared to 25 per cent. of those subjected to radical operation). Only 7 out of the 41 patients had palpable axillary glands, whilst the size of the tumour has varied from »small» to that of an orange.

Histological verification of the diagnosis of cancer has been obtained in 37 cases and is lacking in 4 (no histological examination was made in 1 case: local recurrence after 3 years; histological diagnosis in 1 case: adenofibroma intracanaliculare: no recurrence for 6 years; histological diagnosis in 1 case: no signs of cancer: recurrence after 4 years; and histo-

logical diagnosis in 1 case: adenoma? carcinoma?: no recurrence for 6 years).

This series includes 23, or 56 per cent., alive and free from symptoms and 27, or 66 per cent. alive after 5 years. The corresponding figures for those of our patients who were subjected to radical operation were, respectively, 34 per cent. and 40 per cent. (Table 5).

The above percentage calculation should be taken with reservation, as the series of cases is only small.

Table 7 shows the writers' results and those found by the authors mentioned in the introduction.

Table 7

Writers' Results and those of other Authors in local operation.

	Number of patients	Alive after 5 years
Nohrmann	43	58 %
Mc. Whirter	459	42.9 %
Mustakallio	23	(5 out of 6)
Fitzwilliams	93	66.6 %
Writers' series	41	66 %

Roentgen treatment only: A number of 159 patients have not been operated on.

After 5 years only 5 out of these 159 patients were alive, *i. e.* about 3 per cent. (2 inoperable and 3 not operated on because of advanced age.)

Comments

Operation (radical or local) was made on 330 patients and 159 patients were treated with roentgen exclusively.

After 5 years 30 per cent. of the 489 patients were alive and 20 per cent. were symptomfree.

When comparing this result with that of purely surgical treatment (according to the literature, 30 per cent. alive after 5 years) no demonstrable effect of supplementing roentgen treatment is found in the present series of cases.

Radical operation was performed on 289 patients, 40 per cent. were alive after 5 years. Of these 289 patients 159 had been given pre- and postoperative roentgen treatment and 130 only postoperative roentgen treatment as well.

The results in both series seem to be comparable, as about 45 per cent. of both are in stage 1 and about 55 per cent. are in stage 2. There seems to be no difference between the results obtained in the two series (respec-

tively 37 per cent. and 42 per cent. were alive after 5 years). Local recurrences developed in the cicatrice within 5 years in 11 per cent. of the cases of pre- and postoperative irradiation, and in 17 per cent. of the patients who had been given only postoperative roentgen treatment.

Whilst 34 per cent. remain free from symptoms for 5 years, only 18 per cent. (of 145) had no recurrences for 10 years — a fact which shows how little the result after 5 years can tell us about permanent recovery in cancer of the breast.

A remarkable difference between the results appears when the cases are divided into two groups (comprising 1929 to 1938 and 1939 to 1943), as the former group has 27 per cent., the latter 41 per cent. of cases alive and free from symptoms for 5 years. It is impossible to offer any explanation of this difference.

Forty-one patients were subjected to local operation and were given pre- and postoperative, or only postoperative, roentgen treatment as well. After 5 years 66 per cent. were still alive as compared to 40 per cent. of the cases of radical operation.

Even if the number of cases subjected to local operation is only small, the result is so much in conformity with that of other authors that the question arises whether radical operation is made today in a number of cases where quite as good — perhaps even better — results might be obtained by means of local operation and supplementing irradiation.

After an examination of some of the enormous amount of literature on cancer of the breast, in connection with an analysis of the, comparatively small, number of cases dealt with here, the point immediately arises whether our treatment of mammary cancer has not become stagnant at a not exactly satisfactory level.

The supplementing roentgen treatment does not seem to have caused any signal improvement of the duration of the results of surgical treatment, though the results obtained by other authors seem to show some improvement.

We do not know whether preoperative or postoperative roentgen treatment, or a combination of both forms, is to be preferred. A supplementing roentgen treatment may perhaps reduce the number of local recurrences.

At any rate the results obtained are only poor. In our series only 1 out of 3 of all the patients referred to us is alive and only 1 out of 5 is free from symptoms for 5 years.

The fault may perhaps be that the treatment of cancer of the breast is reduced too much to skeleton form; it may just be possible that a more individualizing treatment of the separate cases might lead to better results.

Today a diagnosed cancer of the breast means radical operation and supplementing irradiation but, as already pointed out, it is possible that a radical operation is superfluous if there are no metastases in the axillary lymph nodes, and it may possibly be of no use — perhaps even harmful — in case there are cancerous axillary glands.

The localization of the tumour to the breast, with the resulting possibilities of metastases to various groups of lymph nodes, is presumably of consequence to the degree of malignancy of the cases and to the effect of therapy — a fact that is not considered today when planning the treatment (FITZWILLIAMS, NOHRMANN).

Our series of cases does not permit an analysis of this, and would also be too small for any safe conclusion to be drawn, but it is unquestionable that this problem requires its ultimate solution.

Cancer of the breast is today one of the most frequent forms of cancer in women — perhaps the most frequent. Our present therapy first of all involves a highly mutilating surgical interference which to many women undoubtedly means a very violent psychic trauma. Nevertheless, *we* are able to cure only from 20 to 30 per cent.

The first step towards better results must undoubtedly consist in a world-wide, uniform statistical dealing with all series of cases of cancer of the breast, such as has been made as far as carcinoma of the cervix is concerned (at HEYMAN's initiative).

SUMMARY

The writers report the results of treatment of cancer of the breast at the Radium Centre in Odense, Denmark, from 1929 to 1943 inclusive. Radical operation was made in 289 cases. After 5 years 40 per cent. of these patients were still alive. Pre- and postoperative roentgen treatment was administered in 159 cases, postoperative treatment only was given in 130 cases; respectively 37 and 42 per cent. were alive after 5 years. Local recurrences occurred within 5 years in 11 per cent. of the cases in which pre- and postoperative treatment had been administered and in 17 per cent. of the patients who had been given only postoperative treatment.

41 patients were subjected to local operation. After 5 years 66 per cent. of these were alive. Though the number of cases in which local operation was made is small and to a certain degree selected, the result is so much in conformity with those of other authors that it is considered justified to raise the question whether our present principles of treatment of cancer of the breast are the right ones.

ZUSAMMENFASSUNG

Die Verfasser berichten über die Erfolge in der Behandlung des Brustkrebses an der Radium-Centrale in Odense, Dänemark, in den Jahren 1929 bis einschliesslich 1943. Die Radikaloperation wurde in 289 Fällen vorgenommen. Nach 5 Jahren betrug die Zahl der Überlebenden 40 prozent. Die prae- und die postoperative Röntgenbehandlung wurde in 159 Fällen durchgeführt, die postoperative Strahlenbehandlung allein in 130 Fällen. Nach 5 Jahren waren noch 37 bzw. 42 Prozent am Leben. Lokale Rezidive traten

innerhalb von 5 Jahren in 11 Prozent der Fälle auf, bei denen die prae- und postoperative Strahlenbehandlung zur Anwendung gekommen war und in 17 Prozent bei den Kranken, die nur die postoperative Bestrahlung erhalten hatten.

Bei 41 Patienten wurde die lokale Operation ausgeführt. Nach 5 Jahren waren von diesen noch 66 Prozent am Leben. Obwohl die Zahl der nur lokal operierten Fälle klein ist und ausserdem bis zu einem bestimmten Grade eine Auswahl darstellt, zeigt der Erfolg eine so grosse Übereinstimmung mit denen anderer Autoren, dass man auf Grund dieser Tatsache durchaus berechtigt sein dürfte, die Frage zu stellen, ob unsere geltenden Richtlinien in der Behandlung des Brustkrebses richtig sind.

RÉSUMÉ

Les auteurs communiquent les résultats du traitement du cancer du sein au Centre du Radium d'Odense, Danemark, de 1929 à 1943 inclusivement. L'opération radicale fut exécutée dans 289 cas. Après 5 ans 40 pour cent de ces malades étaient en vie. 159 patientes furent en outre soumises à un traitement pré- et postopératoire par les rayons de roentgen, et 130 à la seule radiothérapie postopératoire; des premières 37 pour cent étaient vivantes après 5 ans, des secondes 42 pour cent. Des récidives locales survinrent avant 5 ans dans 11 pour cent des cas traités avant et après l'opération, et dans 17 pour cent de ceux qui ne reçurent qu'un traitement postopératoire.

41 malades furent soumises à une opération limiteé. Après 5 ans 66 pour cent d'entre elles vivaient encore. Bien que les cas où l'on a pratiqué une intervention limitée soient peu nombreux et qu'ils aient bénéficié d'une certaine sélection, le resultat obtenu est tellement comparable à celui rapporté par d'autres auteurs qu'on est en droit de se demander si les principes qui gouvernent le traitement actuel du cancer du sein sont justes.

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TRAVAIL DE LA CLINIQUE UNIVERSITAIRE DE DERMATOLOGIE (DIRECTEUR: PROF. W. JADASSOHN), DE L'INSTITUT D'HISTOLOGIE ET D'EMBRYOLOGIE (DIRECTEUR: PROF. E. BUJARD) ET DU RADIUM-INSTITUT (DIRECTEUR: DR. P. WENGER) DE GENÈVE, SUISSE

A PROPOS DE L'EFFET DES RAYONS DE ROENTGEN, DES RAYONS γ, ET DES RAYONS β SUR LA CELLULE EPIDERMIQUE[1,2]

Expériences sur le »Nipple-test» associé à la réaction de Dustin

par

W. Jadassohn, E. Bujard, R. Paillard, P. Wenger et *P. Gaudin*

Dans leur traité intitulé »Action des radiations sur les tissus», A. LACASSAGNE et G. GRICOUROFF (1941) résument ainsi l'évolution des lésions consécutives à une irradiation:

30 minutes déjà après une irradiation suffisante (1,600 à 2,000 r), les mitoses cessent dans les couches germinatives de l'épiderme; celles qui sont en cours dégénèrent et conduisent à la mort cellulaire. Les éléments dégénérés disparaissent en quelques jours par cytolyse; il y a ainsi destruction plus ou moins complète de la couche basale. Les autres couches de l'épiderme, non prolifératives, continuent leur évolution vers la kératinisation et l'épiderme s'amincit peu à peu; finalement il se produit une érosion épidermique qui laisse le derme à nu: radio-épidermite exsudative de REGAUD et NOGIER (1913). Ultérieurement, les mitoses réapparaissent et la régénération de l'épiderme s'effectue; la partie lésée peut retrouver son intégrité. Avec des doses plus faibles (1,200 à 1,600 r), la couche basale n'est pas entièrement détruite, les mitoses reprennent et on n'assiste qu'à une desquamation sèche sans érosion. Avec des doses encore plus faibles (600 à 1,200 r), il y a encore destruction d'un nombre important de cellules basales, mais l'épiderme ne présente pas d'autres lésions apparentes.

Ce tableau succinct de l'action des irradiations néglige un certain nombre de détails importants qu'il paraît utile de relever.

En 1924 et 1925 déjà, G. MIESCHER avait remarqué que la peau humaine peut présenter une ou plusieurs vagues d'érythème accompagnées de lésions épidermiques qu'il a cherchées à l'aide de biopsies; nous retiendrons seulement des altérations coïncidant avec la première et la deuxième vague d'érythème. Après une irradiation unique de 3,000 r,

[1] Soumis à la Réd. le 22 Juin 1950.

[2] Ce travail a bénéficié d'un subside du Centre anticancéreux de Genève.

les modifications épidermiques restent minimes les premiers jours et se résument en général à un léger gonflement cellulaire; toutefois dans quelques cas, l'auteur a pu observer durant cette période des foyers de mitoses normales et anormales. Au début de la deuxième vague d'érythème, vers le huitième jour, l'épiderme aminci présente un polymorphisme nucléaire remarquable; les noyaux sont différents de forme, de volume, de structure; il y a un certain nombre de cellules bi- ou multinucléées et quelques mitoses pathologiques.

Si la peau humaine a été l'objet de nombreux examens, la peau de cobaye n'a été que peu étudiée. A part un ou deux travaux anciens qui ne nous ont pas été accessibles, il n'est possible de citer qu'une note récente de J. FRÉDÉRICQ (1948) et un mémoire de G. MIESCHER (1928) où celui-ci compare l'action de diverses radiations sur la peau humaine et la peau de cobaye.

Dans sa note, J. FRÉDÉRICQ examine l'action d'une dose de 3,000 r appliquée sur la patte postérieure du cobaye. Cette dose entraîne une destruction progressive de l'épiderme, selon une évolution semblable à celle qui est bien connue chez l'homme. L'altération est suivie d'une régénération d'un épiderme épaissi avec apparition de kératohyaline dans les cellules supérieures de la couche épineuse. Au point de vue chimique, la destruction consécutive à l'irradiation est accompagnée d'une diminution de la réaction des groupes -SH au ferricyanure ferrique et au nitroprussiate de soude ammoniacal; ces réactions augmentent par contre fortement au moment de la régénération; l'auteur estime que cette variation des groupes -SH ne dépendrait pas d'une action locale des rayons, mais d'un trouble métabolique général de l'épiderme.

Dans son mémoire, G. MIESCHER note qu'après une irradiation de 800 r, la réaction de l'épiderme de l'oreille de cobaye est faible et l'aspect cytologique presque normal; du deuxième jour au sixième jour, il observe des mitoses pathologiques, en général pycnotiques, et du quatrième au huitième jour, quelques mitoses normales. Une période privée de mitoses vient ensuite, puis les divisions cellulaires réapparaissent vers le vingtième jour, en même temps que l'on peut observer la présence de cellules épidermiques binucléées. Après une irradiation de 2,400 r, la réaction est lente, mais plus nette; au deuxième jour, on trouve des mitoses pycnotiques et des débris de mitoses (Mitosentrümmerzellen) et, du quatrième au sixième jour, des mitoses pycnotiques, quelques mitoses normales et des cellules binucléées. A la suite de l'intervalle acinétique, l'épiderme présente vers la deuxième et la troisième semaine un polymorphisme nucléaire, des cellules bi- ou même trinucléées et des mitoses anormales. Celles-ci sont différentes de celles du début et sont caractérisées surtout par la dispersion chromosomique.

* * *

Il nous a paru intéressant de reprendre l'étude des lésions épidermiques provoquées par les rayons de Roentgen et d'autres radiations ionisantes, en leur associant un facteur stimulant la croissance de la tétine, un oestrogène, et en appréciant l'activité mitotique par la réaction colchicinique de Dustin ou réaction stathmocinétique; cette réaction arrête d'une part l'évolution des cellules en division, permet d'autre part l'entrée en mitoses successives des cellules qui étaient en imminence de division et provoque ainsi une accumulation de mitoses bloquées, qui se seraient achevées

dans les conditions ordinaires. Pour accélérer la croissance épidermique, nous avons utilisé l'Hormoestrol en applications percutanées; cette substance a la propriété de provoquer un épaississement (acanthose) de l'épiderme de la tétine de cobaye mâle. Cet épaississement est lié à une activité proliférative de l'épiderme; dans un même champ de préparation examiné au même grossissement, le nombre des noyaux est augmenté de 50 % en moyenne, après trois applications d'oestrogène; la réaction colchicinique de Dustin est aussi nettement augmentée; elle révèle un plus grand nombre de mitoses que dans l'épiderme d'une tétine témoin, non traitée par l'Hormoestrol. Cette réaction de la tétine mâle vis-à-vis des oestrogènes a été décrite par l'un de nous sous le nom de »Nipple-test». Cet épaississement acanthosique est accompagné de modifications cellulaires sur lesquelles nous reviendrons plus loin (p. 476).

I. — IRRADIATION D'UNE TETINE NORMALE SUIVIE D'APPLICATIONS D'HORMOESTROL, PUIS D'UNE INJECTION DE COLCHICINE (REACTION STATHMOCINETIQUE DE DUSTIN)

A. Action sur les mitoses épidermiques

1. Irradiation avec les rayons de Roentgen

Dans une note précédente, nous avons pu démontrer un effet précoce des rayons de Roentgen sur la cellule épidermique, soit la suppression de la réaction de Dustin sur des tétines de cobayes mâles traitées avec un oestrogène après une irradiation. Notre procédé expérimental a été le suivant:

1. irradiation d'une tétine;

2. traitement des deux tétines (tétine irradiée et tétine témoin) par une solution d'oestrogène, soit une goutte de solution d'Hormoestrol à 2 γ par cm³, un ou plusieurs jours de suite;

3. injection d'une solution de colchicine à la dose de 50 γ pour 100 gr. de cobaye, le lendemain de la dernière application d'Hormoestrol;

4. excision des tétines 9 à 10 heures après l'injection de colchicine, c'est-à-dire au moment où l'accumulation de mitoses bloquées due à cette substance atteint son maximum.

Quant à la technique de l'irradiation, elle a été choisie pour les raisons suivantes: c'est l'habitude à la Clinique de Dermatologie de traiter les petits cancers cutanés par les rayons de Roentgen, à la dose de 2,400 r donnés en trois séances de 800 r chacune, tous les deux jours. L'irradiation se fait presque toujours avec 70,000 volts, 3 milliampères, un filtre de 0.5 mm. d'aluminium, à une distance foyer—peau de 24 cm. La dose de 2,400 r était donc tout particulièrement intéressante pour nous.

a) Effet précoce de 2,400 r donnés en une seule fois

Dans notre première note, nous avons rapporté les résultats obtenus en irradiant la tétine avec 2,400 r (rayons de Roentgen) en une seule séance (ce qui est différent de notre usage clinique) et en employant 5 milliampères au lieu de 3 milliampères; le champ d'irradiation avait un diamètre de 1.5 cm. et la séance une durée de 45 minutes 43 secondes. Immédiatement après l'irradiation d'une tétine, tous les cobayes ont reçu une application d'Hormoestrol sur les deux tétines. Ils ont ensuite été divisés en deux lots:

Le premier lot a reçu, 24 heures après l'irradiation, l'injection bloquante de colchicine et les tétines ont été prélevées 9 à 10 heures plus tard, soit 33 à 34 heures après l'irradiation.

Le deuxième lot a reçu, 24 heures après l'irradiation, une deuxième application d'Hormoestrol et le lendemain une troisième application; le troisième jour, soit 72 heures après l'irradiation, la colchicine a été injectée et les tétines excisées 10 heures après, soit à la quatre-vingt-deuxième heure.

Dans tous les cas: *la réaction colchicinique de Dustin, très positive dans l'épiderme témoin, était supprimée ou presque supprimée dans les tétines irradiées;* l'épiderme irradié ne contient pas ou très peu de divisions cellulaires.

* * *

Dans une nouvelle série d'expériences, nous avons conservé le même schéma expérimental, mais en faisant varier les conditions physiques de l'irradiation par les rayons de Roentgen à la dose de 2,400 r; dans ce but, nous avons modifié l'épaisseur du filtre, le voltage, le milliampérage, la distance foyer—peau et la durée d'exposition.

Tableau I

Rayons de Roentgen	V	mA	Filtre	Dist. F.—P.	Temps
2,400 r	70,000	5	0.5 mm	24 cm	45 min. 43 sec.
2,400 r	70,000	5	3 mm	24 cm	153 min. 27 sec.
2,400 r	70,000	10	0.5 mm	15 cm	9 min.
2,400 r	120,000	9	0.5 mm	15 cm	4 min. 26 sec.
1,200 r	70,000	5	0.5 mm	24 cm	22 min. 49 sec.
1,200 r	120,000	9	0.5 mm	15 cm	2 min. 13 sec.
800 r	70,000	5	0.5 mm	24 cm	15 min. 14 sec.
400 r	70,000	5	0.5 mm	24 cm	7 min. 37 sec.
200 r	70,000	5	0.5 mm	24 cm	3 min. 47 sec.
100 r	70,000	5	0.5 mm	24 cm	1 min. 53 sec.

Les résultats ont été identiques à ceux des expériences déjà citées. C'est-à-dire que la réaction de Dustin a été complètement ou presque complètement supprimée; l'épiderme ne présente presque plus de mitoses.

b) Effet précoce de 1,200 r, 800 r, 400 r, 200 r, donnés en une seule fois

La dose de 1,200 r a été donnée dans des conditions physiques différentes:

70,000 volts, 5 milliampères, 0.5 mm. d'aluminium, distance 24 cm., durée 22 minutes 49 secondes;

120,000 volts, 9 milliampères, 0.5 mm. d'aluminium, distance 15 cm., durée 2 minutes 13 secondes.

Pour les doses plus faibles, les conditions physiques (70,000 volts, 5 milliampères, 0.5 mm. d'aluminium, distance 24 cm.) sont restées les mêmes, mais la durée de l'irradiation a changé selon la dose désirée:

pour	800 r	l'irradiation	a été	de	15	minutes	14	secondes
»	400 r	»	»	»	7	»	37	»
»	200 r	»	»	»	3	»	47	»
»	100 r	»	»	»	1	»	53	»

Comme dans les expériences précédentes, l'irradiation a été suivie d'une à trois applications d'Hormoestrol.

Les résultats ont été les suivants:

1,200 r et 800 r ont un effet très marqué sur la réaction de Dustin qui est considérablement diminuée;

400 r sont un peu moins efficaces, mais ont encore une action très nette;

200 r par contre ne diminuent pas la réaction de Dustin d'une façon constante; il semble que ce soit la dose limite.

Ces résultats sont à rapprocher de ceux obtenus par G. MIESCHER (1928) sur l'oreille du cobaye. Après une irradiation de 2,400 r et de 800 r, il a observé du deuxième au sixième jour un certain nombre de mitoses pathologiques ou pycnotiques et quelques débris de mitoses (Mitosentrümmerzellen).

En résumé, ces expériences montrent qu'après une irradiation de 400 r ou plus, la réaction colchicinique de Dustin diminue; elle devient même presque négative à partir de 1,200 r; les mitoses de l'épiderme sont suspendues.

Il est à noter toutefois que l'épiderme s'est néanmoins épaissi. Cependant la numération des noyaux sur une même surface épidermique de tétine témoin (non traitée à l'Hormoestrol) et de tétine irradiée (traitée 3 jours à l'Hormoestrol) donne le même nombre de noyaux à quelques unités près. L'épaississement épidermique après irradiation n'est donc pas une acanthose véritable (épaississement par augmentation du nombre de cellules), mais une *pseudo-acanthose* (épaississement par augmentation du volume des cellules). Cette pseudo-acanthose est du reste accompagnée d'altérations cellulaires plus importantes que dans l'acanthose vraie, comme nous le décrirons plus loin (p. 479).

c) Effet précoce de 2,400 r donnés en doses fractionnées

Dans les expériences suivantes, la dose de 2,400 r a été fractionnée de diverses façons et dans différentes conditions physiques.

Tableau II

Rayons de Roentgen	Intervalle entre ch. séance	V	mA	Filtre	Dist F. – P.	Temps
3×800 r	24 heures	70,000	5	0.5 mm	24 cm	3×15 min. 14 sec.
3×800 r	24 heures	70,000	5	3 mm	24 cm	3×51 min. 9 sec.
3×800 r	24 heures	70,000	12	0.5 mm	15 cm	3× 2 min. 29 sec.
3×800 r	24 heures	70,000	12	0.5 mm	24 cm	3× 6 min. 20 sec.
3×800 r	24 heures	70,000	2	0.5 mm	24 cm	3×38 min. 5 sec.
3×800 r	24 heures	70,000	3	0.5 mm	24 cm	3×25 min. 23 sec.
3×800 r	24 heures	70,000	6	0.5 mm	24 cm	3×43 min. 31 sec.
3×800 r	24 heures	120,000	9	0.5 mm	15 cm	3× 1 min. 29 sec.
3×800 r	48 heures	120,000	9	0.5 mm	15 cm	3× 1 min. 29 sec.
6×400 r	6 & 18 h.	70,000	5	0.5 mm	24 cm	6× 7 min. 37 sec.
6×400 r	11 & 13 h.	70,000	5	0.5 mm	24 cm	6× 7 min. 37 sec.
12×200 r	24 heures	70,000	3	0.5 mm	24 cm	12× 6 min. 21 sec.

Immédiatement après la dernière irradiation, il a été procédé à l'application d'Hormoestrol et celle-ci a été parfois répétée le deuxième et le troisième jour suivant. L'effet désigné ici par l'adjectif »précoce» est donc en réalité l'effet observé de 1 à 4 jours après la dernière irradiation, et de 4 à 14 jours après la première.

Dans les expériences où la dose de 2,400 r a été obtenue par trois irradiations de 800 r ou par six irradiations de 400 r, les résultats sont les mêmes que lorsque la dose de 2,400 r a été appliquée en une seule fois: *la réaction de Dustin est presque supprimée;* l'épiderme ne contient que de rares mitoses.

Dans les expériences où la dose de 2,400 r a été fractionnée en douze irradiations quotidiennes de 200 r, *la réaction de Dustin est encore nettement diminuée,* mais l'effet est moindre que celui obtenu dans les autres conditions.

2. Irradiation avec les rayons γ et les rayons β

a) Effet précoce de 2,400 r donnés en une seule fois

Il était intéressant de comparer l'action des rayons de Roentgen à celle d'autres radiations ionisantes, telles que les rayons γ et les rayons β à la même dose de 2,400 r.

Cette dose fut donnée en deux heures (120 minutes), c'est-à-dire en un temps situé entre les deux durées extrêmes expérimentées avec les rayons de Roentgen: 45 minutes 43 secondes ou 153 minutes 27 secondes. L'irradiation a été suivie d'une ou trois applications d'Hormoestrol comme dans les expériences avec les rayons de Roentgen.

a) irradiation avec les rayons γ: la source de rayons γ est constituée par 200 mg. de radium élément, en équilibre avec le dépôt actif, et répartie sur une surface de 3 cm². Le rayonnement est filtré par 0.5 mm. de platine. La source est à l'intérieur d'un bloc de plomb. Une fenêtre de 2.5 cm. de diamètre sert de cône d'irradiation. La mesure de l'intensité en r γ a été faite au moyen d'une petite chambre de ionisation de 25 r, d'un »Victoreen condenser r-meter», appareil ayant servi à la mesure des rayons de Roentgen.

Ainsi les mesures γ et Roentgen sont suffisamment comparables. Nous avons trouvé une intensité de 1,200 r γ/heure à la distance de 1 cm. Les cobayes ont été irradiés pendant 2 heures à 1 cm.; ils ont reçu ainsi une dose de 2,400 r γ sur une seule tétine. L'autre tétine protégée par la masse de plomb a reçu suffisamment peu de rayons pour pouvoir servir de témoin.

Dans tous les cas, *la réaction de Dustin a été fortement diminuée ou presque supprimée;* les mitoses sont devenues rares. Les résultats sont semblables à ceux constatés avec les rayons de Roentgen.

β) *irradiation avec les rayons* β: la source de rayons β est constituée par un dépôt de radium (D + E). Elle est exempte de rayonnement γ dur. Le dépôt est réparti sur une surface de 3 cm². Le rayonnement est filtré par une feuille de matière plastique de 2.3 mg. par cm², laissant passer la presque totalité du rayonnement β. La source est entourée de plomb de manière à arrêter tout son rayonnement à l'exception d'une fenêtre de 2.5 cm. de diamètre servant de cône d'irradiation. La mesure de l'intensité en r β a été faite par comparaison avec la source étalonnée de rayons γ. Cette comparaison a été effectuée au moyen d'une grande chambre de ionisation de 1,000 cm³ ayant une paroi de 2.5 mg. par cm². Nous avons trouvé une intensité de 1,200 r β /heure à la distance de 1 cm. Les cobayes ont été irradiés pendant 2 heures à 1 cm.; ils ont reçu ainsi une dose de 2,400 r β sur une seule tétine. L'autre tétine protégée par la masse de plomb a servi de témoin.

Dans tous les cas, *la réaction de Dustin a été supprimée ou presque.* Les résultats sont les mêmes que ceux obtenus avec les rayons de Roentgen ou les rayons γ.

En résumé, l'effet précoce d'une dose de 2,400 r (dose supérieure aux doses limites) donnée en une seule séance et en des temps presque égaux, est le même pour les rayons de Roentgen, les rayons γ et les rayons β. La capacité de division des cellules épidermiques est inhibée.

Ces constatations ne sont pas en contradiction avec l'idée que l'effet dépend uniquement de l'ionisation produite par les rayons, indépendamment du genre de rayons qui provoquent cette ionisation.

b) Effet précoce de 2,400 r donnés en doses fractionnées

Les dispositifs expérimentaux sont les mêmes que ceux décrits ci-dessus, seul le facteur temps a varié.

Tableau III

Rayons γ	Interv. entre ch. séance	Temps
3×800 r	24 heures	3×40 min.
12×200 r	24 heures	12×10 min.
Rayons β	**Interv. entre ch. séance**	**Temps**
3×800 r	24 heures	3×40 min.
3×800 r	48 heures	3×40 min.
12×200 r	24 heures	12×10 min.

Ces expériences ont donné des résultats superposables à ceux obtenus avec les rayons de Roentgen appliqués en doses fractionnées.

B. Modification histologique de l'épiderme

1. Epiderme de la tétine normale

L'épiderme est mince, composé de trois ou quatre assises cellulaires seulement. La couche basale, régulière, contient des noyaux ronds ou ovoïdes, serrés les uns à côté des autres; les mitoses y sont localisées. La réaction colchicinique n'accumule que très peu de divisions; elles sont du reste toutes pycnotiques (fig. 1). Ces mitoses bloquées ont l'aspect habituel: une masse chromosomique dans une cellule arrondie à cytoplasme clair, souvent vacuolisé. Les noyaux au repos sont de taille légèrement inégale et il y a parfois de très rares cellules binucléées. La couche épineuse comprend en général deux rangées de cellules à noyaux ronds, de volumes légèrement inégaux, et de rares cellules binucléées. La couche granuleuse, enfin, est réduite à une seule assise de cellules aplaties.

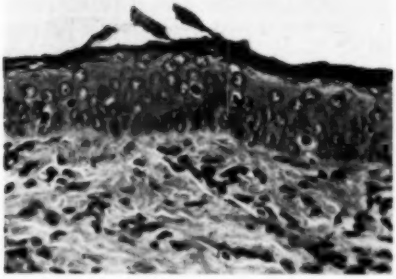

Fig. 1. Tétine non traitée, injection de colchicine : rares mitoses.

2. Epiderme de tétines traitées par l'Hormoestrol

La réaction de l'épiderme de tétines de cobaye mâle ayant reçu une ou plusieurs applications d'Hormoestrol est, avons-nous dit, un épaississement avec augmentation du nombre des noyaux et du nombre des mitoses accumulées par la colchicine; la réaction stathmocinétique de Dustin est positive, c'est-à-dire augmentée.

Cet épaississement de l'épiderme est accompagné de modifications cellulaires portant les unes sur le noyau, les autres sur le cytoplasme. Les noyaux sont d'une façon générale un peu plus volumineux que dans l'épiderme normal; l'inégalité nucléaire est plus marquée et le nombre de cellules binucléées devient parfois d'une certaine importance. Les noyaux épidermiques, réguliers chez les témoins, prennent des formes diverses, allant du noyau arrondi au noyau en forme d'ellipse allongée, et possèdent des tailles nettement inégales. Les noyaux ratatinés c'est-à-dire les noyaux condensés et de formes un peu anguleuses, qui sont rares dans

l'épiderme normal, sont un peu plus nombreux dans l'épiderme épaissi et plusieurs tendent à devenir complètement pycnotiques, réduits à un petit globe chromatique homogène. Ces modifications, déjà appréciables après une seule application d'Hormoestrol, s'accentuent après plusieurs applications; le nombre des cellules binucléées augmente, l'inégalité nucléaire s'aggrave et il apparaît quelques gros noyaux dont la chromatine est diminuée.

La couche basale, simple et à noyaux régulièrement disposés dans l'épiderme normal, est stratifiée par suite de la multiplication cellulaire et les mitoses y sont réparties à plusieurs niveaux. De plus, elle tend à devenir un peu irrégulière; les espaces intercellulaires s'élargissent parfois légèrement et les ponts intercellulaires deviennent plus faciles à observer. Les cellules de la couche épineuse tendent aussi à grossir et ce début d'hypertrophie renforce l'épaississement consécutif à la multiplication cellulaire. La couche granuleuse s'épaissit aussi et s'étend sur trois ou même quatre assises cellulaires (fig. 2).

Après la réaction colchicinique, qui permet de mettre en évidence la stimulation hormonale (B. Bastenie et S. Zylberszac, 1938), les mitoses sont très nombreuses; l'action de l'oestrogène est manifeste et a déclenché d'abondantes divisions qui ont été bloquées et accumulées par la colchicine. Ces mitoses sont pour la plupart très condensées, pycnotiques, semblables à celles plus rares obtenues dans l'épiderme non traité; toutefois les cellules finement vacuolisées qui les contiennent sont un peu plus grandes après le traitement à l'oestrogène que chez les témoins. A côté de ces mitoses pycnotiques, quelques autres sont moins serrées et présentent parfois un peu de dispersion de quelques chromosomes: ces mitoses anormales sont de même ordre que les mitoses altérées observées par G. Miescher (1928) dans l'épiderme de l'oreille de cobaye après une irradiation et que cet auteur rapproche de l'effet secondaire d'Alberti et Politzer. En fait, ces mitoses anormales sont l'expression d'une altération cellulaire moindre que les mitoses pycnotiques; elles peuvent être observées dans les cellules les plus diverses sous l'effet de facteurs très différents, lorsque l'action de ceux-ci est inefficace pour provoquer une condensation totale de la figure de division. A côté de ces mitoses plus ou moins gravement altérées, on peut trouver, rarement du reste, une ou deux prophases d'apparence presque normale.

Les modifications cellulaires décrites ci-dessus sont celles que l'on observe en général après trois applications quotidiennes d'Hormoestrol. Leur importance est variable et l'on constate à ce sujet d'assez grandes différences individuelles entre les cobayes mâles expérimentés.

Des applications plus nombreuses ne changent que peu ce tableau; l'épiderme continue à s'épaissir tant par son activité mitotique que par l'hypertrophie modérée de ses cellules, tandis que les assises de la couche

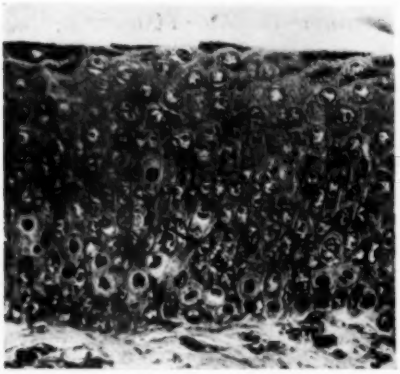

Fig. 2. Trois applications quotidiennes d'Hormoestrol, injection de colchicine: acanthose, nombreuses mitoses.

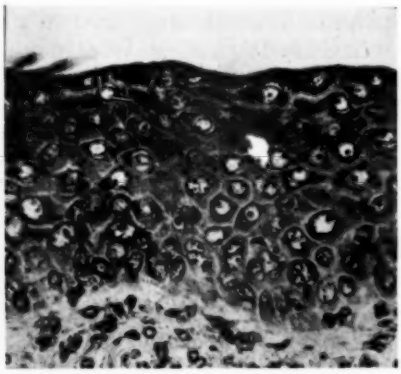

Fig. 3. Irradiation: 2,400 r (rayons de Roentgen), trois applications quotidiennes d'Hormoestrol, injection de colchicine: pseudo-acanthose, très rares mitoses.

granuleuse augmentent en nombre et finissent par intéresser quatre rangs de cellules aplaties (voir fig. 3 et 4 dans W. JADASSOHN et H. E. FIERZ).

Il est à noter que le plus grand nombre de mitoses semble correspondre à trois applications d'oestrogène. Après dix applications d'Hormoestrol, le nombre des divisions est en général diminué, comme s'il y avait une fatigue de l'activité mitotique chez des cellules épidermiques. Après trente et soixante applications d'Hormoestrol, le nombre des mitoses ne s'accroît pas à nouveau.

Une dernière remarque, dans le mince épithélium normal, il n'y a pas de papilles dermiques. Parallèlement à l'épaississement de l'épiderme sous l'effet de l'oestrogène, il y a aussi une différenciation de papilles; celle-ci commence le plus souvent après trois applications, puis augmente progressivement de telle sorte qu'après soixante applications, l'épiderme est pénétré par de longues et minces papilles dermiques.

En résumé, l'épaississement de l'épiderme de la tétine traitée par un oestrogène est la somme de divers phénomènes: une multiplication cellulaire très active, une augmentation modérée du volume de ses éléments.

3. Epiderme des tétines irradiées (rayons de Roentgen, rayons γ et rayons β) traitées par l'Hormoestrol

Après irradiation, la réaction colchicinique de Dustin est fortement diminuée, ce qui signifie que la capacité de l'épiderme à se diviser par

voie mitotique est considérablement amoindrie; l'épiderme ne réagit plus à l'oestrogène par une activité essentiellement prolifération.

Toutefois, la comparaison de tétines examinées au quatrième jour après l'irradiation, les unes traitées trois fois par l'Hormoestrol, les autres laissées trois jours sans traitement, montre dans ces dernières une extinction totale de la réaction de Dustin, c'est-à-dire qu'il n'y a aucune mitose, tandis qu'après traitement à l'oestrogène, un petit nombre de mitoses peut exister; l'Hormoestrol peut révéler une faible capacité de division, qui passerait inaperçue sans ce facteur de stimulation. Les mitoses ont du reste les mêmes qualités que celles décrites après l'action de l'Hormoestrol seul; la plupart, très condensées, sont pycnotiques; quelques autres, moins serrées, présentent parfois un peu de dispersions chromosomiques; de rares prophases enfin sont d'apparence normale.

L'épiderme est épaissi à peu près au même degré que celui qui n'a pas été irradié, malgré le nombre relativement petit de mitoses, révélé par la colchicine. La numération des noyaux dans un même champs de préparation examiné au même grossissement, donne le même nombre de noyaux, à quelques unités près, dans les tétines irradiées et traitées par trois applications d'Hormoestrol et dans les tétines témoins non traitées par l'oestrogène. L'épaississement de l'épiderme, sous l'effet de l'Hormoestrol après irradiation, n'est donc pas une acanthose vraie, mais une pseudo-acanthose consécutive à une hypertrophie simple des cellules épidermiques (fig. 3). On constate, en particulier, une augmentation du volume des cellules épineuses, dont le cytoplasme prend souvent un aspect fibrillaire, qui semble pouvoir être attribué à une imbibition cellulaire rendant plus visibles les tonofibrilles. De plus, les cellules sont souvent un peu écartées ce qui met en évidence les ponts protoplasmiques difficiles à voir sur un épiderme normal de tétine de cobaye. Dans quelques cas cela peut aussi s'observer au niveau des couches profondes, qui présentent un certain désordre et dont les noyaux sont souvent volumineux. L'inégalité nucléaire, qui apparaît à la suite d'applications d'Hormoestrol sur une tétine normale, est éxagérée, lorsque ces applications sont faites sur une tétine irradiée. Il apparaît un nombre variable de gros noyaux, les uns arrondis, les autres elliptiques, et parfois de très gros noyaux, en général peu chromatiques, avec un énorme nucléole polymorphe (arrondi, triangulaire, fusiforme, en bissac, etc.). Ces altérations épithéliales sont, d'une façon générale, de même nature que celles obtenues par l'application d'Hormoestrol sur la tétine normale, mais leur valeur relative est changée et leur importance augmentée.

Les altérations que nous venons de décrire sont celles que l'on observe en général après une irradiation de 2,400 r suivie d'une à trois applications d'Hormoestrol. Leur importance est en partie fonction de la dose de rayons; en effet, avec des doses faibles (200 r), on n'observe

qu'une diminution relativement faible du nombre des mitoses; avec 400 r, cette diminution est plus nette et l'inégalité nucléaire s'accentue un peu dans les couches profondes de l'épiderme; avec 800 r commencent à apparaître les signes d'hypertrophie de la couche épineuse. Il faut toutefois faire la réserve que l'on observe des différences individuelles importantes chez les divers cobayes et que, dans les mêmes conditions expérimentales, le degré des altérations peut être très différent, ce qui rend difficile d'établir une relation précise entre la dose et la gravité des modifications épidermiques.

En résumé, si l'action de l'Hormoestrol est caractérisée sur l'épiderme de tétine normale par une activité proliférative, compliquée d'une faible hypertrophie cellulaire lorsque les applications sont suffisamment répétées, elle relève surtout de ce phénomène d'hypertrophie cellulaire avec gonflement nucléaire, associé à un léger oedème intercellulaire, si les tétines ont été irradiées au préalable.

Ces altérations sont nettes après trois applications quotidiennes d'Hormoestrol; elles semblent tantôt s'atténuer, tantôt s'aggraver, si les applications sont répétées plus longtemps. En effet, chez trois cobayes ayant reçu dix applications d'Hormoestrol après une irradiation de 2,400 r, les lésions de l'épiderme sont considérablement augmentées; les couches profondes sont désorganisées et réduites par place à quelques gros éléments dont le noyau est altéré; l'hypertrophie des couches épineuses est compliquée d'une vacuolisation plus ou moins importante selon les régions (fig. 4) et, dans un cas, de foyers de nécrose. Chez l'un des cobayes, les divisions ont complètement disparu, tandis que chez les deux autres, le nombre des mitoses est considérablement augmenté par comparaison avec les tétines témoins; il semble qu'il s'agisse alors d'un phénomène de régénération. Chez trois autres cobayes expérimentés dans les mêmes conditions (2,400 r et dix applications d'Hormoestrol), les modifications de l'épiderme ne sont guère plus marquées que chez les cobayes n'ayant reçu que trois applications d'Hormoestrol et le nombre de mitoses est nettement diminué.

Après trente applications quotidiennes d'oestrogène, il y a une diminution de mitoses, mais les autres effets de l'irradiation ne se font plus guère sentir. Enfin, après soixante applications d'Hormoestrol, les deux tétines, témoin et irradiée, sont semblables et ne présentent toutes deux que les caractères que nous avons décrits pour l'acanthose d'origine oestrogénique.

Les modifications épidermiques consécutives à l'action de l'oestrogène après irradiation sont les mêmes quelle que soit la qualité des rayons utilisés: rayons de Roentgen, rayons γ et rayons β. Les petites différences de degré d'altérations que nous avons notées parfois peuvent relever aussi bien de différences individuelles de réaction, comme nous en avons

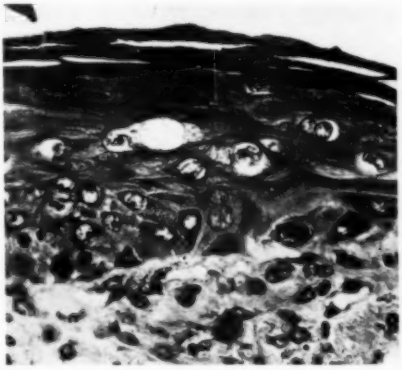

Fig. 4. Irradiation: 2,400 r (rayons de Roentgen), dix applications quotidiennes d'Hormoestrol, injection de colchicine: graves altérations (non constantes).

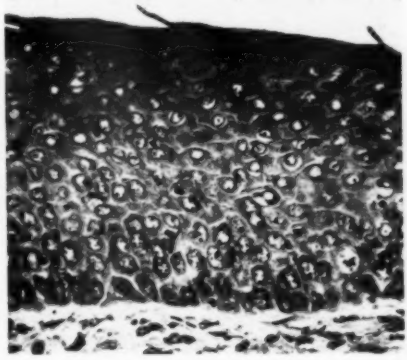

Fig. 5. Acanthose irradiée: 2,400 r (rayons de Roentgen), injection de colchicine le lendemain: rares mitoses.

observé vis-à-vis de l'action de l'Hormoestrol sur la tétine normale, que de nuances dans l'effet des diverses radiations utilisées. De nouvelles expériences permettront peut-être de résoudre cette question.

Une dernière remarque: les modifications épidermiques que nous avons constatées après l'action associée d'une irradiation et d'un oestrogène ne sont pas particulières à ce mode expérimental. Elles ont déjà été observées par G. MIESCHER en 1928 qui a signalé dans l'épiderme la présence de noyaux volumineux, de cellules binucléées et d'un gonflement cellulaire comme phénomènes tardifs consécutifs à l'action de la chaleur, des rayons de Roentgen etc.

II. — IRRADIATION D'UNE TETINE ACANTHOSIQUE, SUIVIE OU NON D'APPLICATIONS D'HORMOESTROL, PUIS D'UNE INJECTION DE COLCHICINE (REACTION STATHMOCINETIQUE DE DUSTIN)

Dans toutes les expériences précédentes, nous avons irradié une tétine normale et fait suivre l'irradiation d'applications d'oestrogène (Hormoestrol) dans le but d'augmenter le nombre des divisions dans l'épiderme.

Pour cette nouvelle série d'expériences, notre procédé expérimental a été le suivant:

1) traitement des deux tétines par la solution d'Hormoestrol, répété trois jours consécutifs pour provoquer l'acanthose;

2) irradiation d'une tétine avec 2,400 r;

3) en général nouveau traitement par la solution d'oestrogène une ou trois fois;
4) injection de la solution de colchicine;
5) excision des tétines 9 à 10 heures après l'injection de colchicine.

Les doses d'Hormoestrol et de colchicine ont été les mêmes que dans nos expériences précédentes.

A. Action sur les mitoses de l'épiderme acanthosique

Effet d'une irradiation avec 2,400 r

Les tétines furent irradiées dans des conditions physiques diverses.

Tableau IV

Rayons de Roentgen	V	mA	Filtre	Dist. F.—P.	Temps
2,400 r	70,000	5	0.5 mm	24 cm	45 min. 43 sec.
3×800 r	70,000	5	0.5 mm	24 cm	3×15 min. 14 sec.
3×800 r	70,000	5	3 mm	24 cm	3×51 min. 9 sec.
6×400 r	70,000	5	0.5 mm	24 cm	6× 7 min. 37 sec.
12×200 r	70,000	3	0.5 mm	24 cm	12× 6 min. 21 sec.
1,200 r	70,000	5	0.5 mm	24 cm	22 min. 51 sec.

Rayons γ	Temps
12×200 r	12×10 min.

Rayons β	Temps
2,400 r	2 heures
12×200 r	12×10 min.

Dans ces expériences, les résultats sur la division cellulaire furent semblables à ceux obtenus précédemment: *il n'y a pas de différence appréciable dans l'effet de l'irradiation d'une tétine normale ou d'une tétine acanthosique;* 2,400 r donnés en une séance, 2,400 r fractionnés en trois ou six séances, ou 1,200 r donnés en une séance rendent la réaction de Dustin négative ou presque négative. 2,400 r fractionnés en douze séances quotidiennes de 200 r chacune sont moins efficaces; la réaction de Dustin est seulement diminuée sur la tétine acanthosique comme sur la tétine normale.

En résumé, nos expériences montrent que l'épiderme acanthosique se comporte vis-à-vis des rayons de Roentgen, des rayons γ et des rayons β de la même façon que l'épiderme normal.

B. Modifications histologiques de l'épiderme

Les diverses modifications épidermiques que nous avons observées après irradiation d'une tétine rendue acanthosique sont les mêmes

que celles que nous avons décrites après irradiation d'une tétine normale et leur degré paraît de même valeur.

Comme nous venons de le dire, le nombre des mitoses a diminué; celles qui existent sont pour la plupart pycnotiques; quelques-unes sont toutefois moins serrées et présentent plusieurs anomalies dans la distribution de leurs chromosomes; quelques prophases, enfin, sont d'apparence presque normale. Ce tableau des mitoses ne diffère guère de celui qui résulte de l'action de l'oestrogène appliqué après l'irradiation (fig. 5).

Les noyaux déjà hypertrophiés sous l'influence de l'Hormoestrol ont encore gonflé et quelques-uns sont devenus particulièrement volumineux. Les cellules binucléées ne sont guère plus fréquentes, mais l'état de leur noyau paraît plus souvent discordant; l'un des noyaux est normal, tandis que l'autre est tantôt gonflé, tantôt ratatiné. Ce ne sont là toutefois que de petites différences auxquelles il ne faut pas attacher une importance trop grande.

Sur deux cobayes, les applications quotidiennes d'Hormoestrol furent répétées sept fois après l'irradiation, ce qui porte à dix le nombre total de ces applications. L'épiderme des deux tétines irradiées présente de graves altérations: les couches basales sont désorganisées et réduites à quelques grosses cellules plus ou moins dégénérées; les mitoses ont complètement disparu; il y a d'énormes noyaux pâles; les couches moyennes montrent enfin une certaine tendance à la vacuolisation. Ces altérations survenues 7 jours après l'irradiation sont de même ordre, quoique d'un degré un peu moindre que celles que nous avons déjà observées lorsque l'irradiation d'une tétine normale a été suivie de dix applications quotidiennes d'oestrogène.

Il est donc permis de conclure que les réactions de l'épiderme sont les mêmes, que l'oestrogène ait été appliqué avant ou après l'irradiation ou avant et après celle-ci, comme nous l'avions fait dans notre première série d'expériences.

Or la cellule en voie de division est réputée particulièrement sensible à l'action de radiations et c'est la raison qui nous a incités à irradier des tétines dont l'épiderme est particulièrement riche en mitoses et présente une croissance supérieure à la normale.

Nos expériences n'ont pas démontré une différence de sensibilité vis-à-vis des radiations. La dose fractionnée de douze fois 200 r semble être, dans nos conditions expérimentales, la dose limite pour l'épiderme de la tétine, que l'irradiation ait été faite sur une tétine normale ou sur une tétine acanthosique, puisque ce fractionnement de la dose diminue moins la réaction de Dustin que si les 2,400 r sont appliqués en une fois. On aurait pu penser que cette même dose fractionnée aurait eu un effet plus marqué sur l'épiderme acanthosique que sur l'épiderme normal; ce n'a pas été le cas.

En résumé, nos expériences parlent dans le même sens que REISS: »Tout se passe comme si ce n'était pas l'activité d'une cellule dans les conditions expérimentales, mais l'activité qu'elle aurait dans les conditions habituelles, son activité potentielle pour ainsi dire, qui détermine sa sensibilité.»

On peut donc conclure que la cellule épidermique de la tétine normale a la même potentialité mitotique et réagit de la même façon vis-à-vis des radiations que la cellule épidermique de l'acanthose due à un oestrogène.

III. — DISCUSSION GENERALE

L'association d'une irradiation avec l'action d'un oestrogène stimulant la croissance de l'épiderme permet de déceler dans la cellule épidermique des modifications qui échappent à l'observation dans d'autres conditions.

L'application d'un oestrogène tel que l'Hormoestrol sur une tétine normale augmente le nombre des mitoses et elle a pour conséquence un épaississement progressif de l'épiderme, une acanthose. Celle-ci est due essentiellement à l'accroissement du nombre des éléments, mais elle est accompagnée cependant d'une légère hypertrophie cellulaire qui se traduit par une augmentation de la taille des cellules, par une augmentation plus ou moins marquée du volume des noyaux des couches profondes, par une exagération de l'inégalité nucléaire (qui existe déjà faiblement dans l'épiderme normal) et par une augmentation du nombre des assises cellulaires qui constituent la couche granuleuse. Cet épaississement de l'épiderme est complété par la différenciation de papilles dermiques qui le pénètrent secondairement.

L'interprétation de l'augmentation du nombre des mitoses sous l'effet de l'oestrogène est délicate; il semble toutefois que l'explication la plus plausible soit celle-ci: l'oestrogène agirait sur la croissance de l'épiderme qu'il augmente en modifiant vraisemblablement le métabolisme des cellules. L'augmentation de volume de ces dernières, leur hypertrophie simple, les conduit à la division qui se déclenche dès qu'un certain équilibre est dépassé. C'est ainsi que l'action proliférative corrigerait l'effet hypertrophique de l'oestrogène. La multiplication cellulaire apparaît alors comme le facteur principal de l'acanthose.

L'action des rayons peut être expérimentée avant ou après l'application d'oestrogène et les résultats sont équivalents dans ces deux conditions. Après une irradiation avec une dose de 2,400 r, on observe une suspension des divisions cellulaires telle que la réaction colchicinique de Dustin devient négative. L'application d'un oestrogène, l'Hormoestrol,

provoque toutefois un certain nombre de mitoses qui témoignent que l'épiderme possède encore après irradiation une faible capacité de division, qui resterait ignorée sans cette stimulation. Le même résultat est obtenu que la dose de 2,400 r soit donnée en une seule séance ou fractionnée en plusieurs séances; toutefois lorsque le fractionnement est poussé jusqu'à douze séances quotidiennes de 200 r, la réaction de Dustin est encore diminuée mais de façon moins nette que dans les autres cas. Des doses inférieures à 2,400 r ont une action décroissante et il semble que la dose unique de 200 r représente la dose limite, car elle ne diminue pas la réaction de Dustin de façon constante.

Si l'on accepte l'explication ci-dessus de l'effet mitogénétique de l'oestrogène sur la tétine normale, l'action de cet oestrogène après irradiation relèverait du fait que l'augmentation du volume cellulaire due à l'Hormoestrol ne serait pas gênée par l'irradiation, tandis que le mécanisme de la division est altéré au point de rendre celle-ci impossible ou tout au moins difficile; la croissance cellulaire se poursuit donc sans aboutir à la division; il en résulte une augmentation anormale du volume du noyau, qui présente du reste des altérations de structure, et une hypertrophie plus ou moins générale des cellules épidermiques. L'hypertrophie simple a pris le pas sur la multiplication cellulaire; l'épaississement de l'épiderme devient une pseudo-acanthose, sans augmentation appréciable du nombre des noyaux.

L'action de l'Hormoestrol seul diffère donc de l'action associée de cet oestrogène avec l'irradiation en ce sens que l'oestrogène provoque une hypertrophie simple sans empêcher les mitoses, en les favorisant au contraire, tandis que l'irradiation empêche la division cellulaire de telle sorte qu'il ne reste que l'effet hypertrophique de l'oestrogène.

Si les applications de l'oestrogène sont répétées un nombre de fois suffisant (sept à dix fois environ) après l'irradiation, elles peuvent entraîner parfois, pas toujours, des modifications plus graves de l'épiderme, soit une désorganisation des couches basales et une vacuolisation plus ou moins marquée de la couche épineuse. Il est à noter toutefois que ces altérations surviennent quelques jours après l'irradiation et qu'il est difficile de dire si elles sont simplement la conséquence tardive de celle-ci ou si l'oestrogène a aggravé par son action stimulatrice des lésions non apparentes.

Quoi qu'il en soit, après trente et soixante applications, l'épiderme irradié a repris les caractères d'un épiderme acanthosique d'origine oestrogénique.

RÉSUMÉ

L'action associée sur la tétine du cobaye mâle d'une irradiation et d'un oestrogène a été étudiée et contrôlée par la réaction colchicinique de Dustin. L'irradiation (rayons de Roentgen, rayons γ et rayons β) avec une dose suffisante inhibe les mitoses épidermiques dans les tétines traitées ensuite par l'oestrogène comme dans les tétines non traitées par cette substance. Cet effet de l'irradiation est plus démonstratif lorsque l'irradiation est combinée avec l'application d'un oestrogène, car la tétine témoin montre dans ce cas davantage de mitoses. Une dose de 200 r n'a pas d'effet appréciable; par contre, une dose de 400 r et des doses plus élevées se montrent actives; 2,400 r donnés en une seule séance, sous différentes conditions physiques et par conséquent en des laps de temps très différents (4 minutes 26 secondes à 153 minutes 27 secondes) sont efficaces, quel que soit le genre de rayons (Roentgen, γ, β). On n'observe une diminution de l'effet de 2,400 r que si le fractionnement de cette dose est poussé jusqu'à douze doses quotidiennes de 200 r. L'irradiation a la même action sur les tétines rendues au préalable acanthosiques par applications d'oestrogène.

L'oestrogène provoque un épaississement de l'épiderme de la tétine, une acanthose; cet épaississement est consécutif à une multiplication active des cellules et à un léger degré d'hypertrophie simple de celles-ci. L'application d'oestrogène après irradiation provoque l'apparition d'un certain nombre de mitoses, qui montrent que la capacité de division des cellules épidermiques n'est pas totalement abolie par les rayons. Ces mitoses peu nombreuses ne suffisent pas à expliquer l'épaississement de l'épiderme après irradiation.

L'action de l'oestrogène après irradiation se traduit par une hypertrophie simple portant à la fois sur les noyaux et sur les cytoplasmes et par un certain degré d'imbibition de l'épiderme; il s'agit alors d'une pseudo-acanthose.

SUMMARY

The combined action of irradiation therapy and treatment by oestrogenic hormones on the nipple of the male guinea-pig has been studied and controlled by Dustin's colchicinic reaction. Roentgen, γ and β rays administered in sufficiently large doses inhibit mitosis of the epidermic cells of the nipple. This action is also maintained if oestrogenic hormones are administered after irradiation. This effect of irradiation is more evident when the irradiation is combined with the application of an oestrogen, as the control nipple presents more mitoses. A dose of 200 r has no appreciable effect; on the other hand, 400 r or still larger doses are effective. A single dose of 2,400 r given under varying physical conditions and consequently also for varying lengths of time (from 4 minutes 26 seconds to 153 minutes 27 seconds) is effective regardless of the type of rays used (Roentgen, γ or β). However, the effect of 2,400 r decreases if this total dose is applied in fractional doses of 200 r per day over twelve days. Irradiation has the same effect on the nipple showing acanthosis produced by the administration of oestrogenic hormones prior to irradiation.

Oestrogenic hormones cause a thickening of the epidermis of the nipple, *i. e.* acanthosis, through mitosis and a mild degree of simple hypertrophy of the cells. A few mitotic figures are also seen if oestrogenic hormones are administered after irradiation. It is evident that irradiation therapy does not totally destroy the capacity of the epidermic cells to divide. However, the number of mitotic figures is too small to explain the thickening of the epidermis after irradiation.

The action of oestrogenic hormones administered after irradiation produces a simple hypertrophy involving similarly the nuclei and the cytoplasm, and a certain degree of imbibition of the epidermis, the combination of which we call pseudo-acanthosis.

ZUSAMMENFASSUNG

Unter Zuhilfenahme der Colchicin-Reaktion nach Dustin wird die kombinierte Wirkung von Bestrahlung und Oestrogen-Behandlung auf die Epidermis der Zitze des männlichen Meerschweinchens untersucht. Durch die Bestrahlung (Röntgen, γ und β Strahlen) werden, eine genügende Dosis vorausgesetzt, die epidermalen Mitosen in den Zitzen gehemmt. Diese Hemmung ist sowohl in den Zitzen nachweisbar, die nachher mit Oestrogen behandelt wurden, als auch in denjenigen, bei denen dies nicht der Fall war. Bei den nachher mit Oestrogen behandelten Zitzen ist die Hemmung aber viel auffälliger, weil die mit Oestrogen behandelten Kontrollzitzen sehr viele Mitosen aufweisen. Eine Dosis von 200 r ergibt keinen deutlichen Effekt, dagegen sind Dosen von 400 r und mehr sicher wirksam. Werden Dosen von 2,400 r in einer Sitzung unter verschiedenen physikalischen Bedingungen und folglich auch in sehr verschieden langen Bestrahlungszeiten (4 Min. 26 Sek. bis 153 Min. 27 Sek.) verabfolgt, so ist der Effekt der gleiche und unabhängig von der Art der verwendeten Strahlen (Röntgen, γ und β Strahlen). Eine Verringerung des Effektes von 2,400 r wird nur dann beobachtet, wenn die Gesamtdosis in 12 Einzeldosen von je 200 r, die täglich verabfolgt werden, fraktioniert wird. Der Effekt der Bestrahlungen ist der gleiche, wenn Zitzen verwendet werden, die vorher durch Oestrogenapplikation akantotisch gemacht wurden.

Oestrogene bewirken eine Verbreiterung der Epidermis der Zitze, eine Akantose. Diese Verbreiterung beruht auf einer Vermehrung der Zellen und auf einer geringen einfachen Zellhypertrophie. Wird nach der Bestrahlung ein Oestrogen appliziert, so bewirkt dies das Auftreten einer gewissen Zahl von Mitosen. Die Teilungsfähigkeit der epidermalen Zellen wurde also durch die Bestrahlung nicht völlig aufgehoben. Die relativ seltenen Mitosen genügen aber nicht zur Erklärung der Verbreiterung der Epidermis nach der Bestrahlung.

Das nach der Bestrahlung applizierte Oestrogen bewirkt eine einfache Hypertrophie der Zellkerne und der Cytoplasmen und eine gewisse Imbibition der Epidermis. Es handelt sich also um eine Pseudoakantose.

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FROM THE RADIUM CENTER IN COPENHAGEN, DENMARK (DIRECTOR: JENS NIELSEN)

BIOELECTRIC POTENTIALS IN UTERINE CARCINOMA[1, 2]

by

Svend Dalgaard and *Jørgen E. Thygesen*

In 1947 LANGMAN and BURR briefly reported the results of measurements of bioelectric potentials on patients suffering from carcinoma of the uterine cervix (1). Their series comprised 14 cases all of which showed negativity of the cervix, whereas among a control series of 15 patients with benign lesions or no abnormalities all but 3 showed positivity of the cervix. In a later publication (2) the same workers reported the results of measurements on a larger series. Negativity of the cervix was found in 98.7 per cent. of all cases (a total of 75) in which there was clinical and histological proof of malignancy.

It was therefore felt that it would be interesting to carry out similar studies in a series of proven cases of uterine carcinoma, since such a phenomenon might afford a supplement to the clinical and histological examinations in current use.

Technique

The procedure is that used by LANGMAN and BURR. Non-polarizable silver-silver chloride electrodes are used. They are produced (3) by chlorinating pure silver wire in a molar solution of hydrochloric acid.

Each silver wire is made an anode in a cell with a platinum wire as cathode, all cells are connected in series, and a current of 10—20 ma. is passed through them for about 10 minutes. Electrodes produced this way can, with some care, be made reproducible within 1 millivolt. The chlorinated electrodes are placed in open glass tubes and fixed with a ring of plastic. The upper end of each tube is closed with paraffin. The glass tubes are filled with 0.9 per cent. saline, the concentration of which

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is not critical but must be exactly the same in both electrodes. The open end of each tube is plugged with cotton wool through which the saline is brought into contact with the skin or mucosa.

Since it is essential that no significant current is drawn from the specimen under test the instrument used must possess a very high input impedance as compared with the resistance in the test object which latter amounts to a few kilo-ohms (4). The tube potentiometer used in the experiments had an input impedance of 100 megohms (Radiometer PHM 1).

Position of electrodes: The patient lies comfortably and well relaxed on a couch adequately insulated from the ground (rubber foot pieces, cork floor). The vaginal electrode is inserted so that its tip is situated behind the cervix in the posterior lacuna. The reference electrode is placed so that the plug of cotton, soaked in physiological saline is in contact with the skin slightly above the symphysis pubis. Readings are made every minute for 10—15 minutes, and after the measurements have been finished, the electrodes are checked by measurement of their potential difference when they are both immersed in the same physiological saline.

Authors' Measurements

Measurements were carried out on 29 patients with cervical carcinoma of stages I—IV or carcinoma of the uterine corpus and on one ovarian carcinoma, all of which had been proved by clinical and histological examination. With a few exceptions the measurements were made prior to the initiation of treatment. A few irradiations, however, did not seem to influence the potential.

Case No.	Age	Clinical diagnosis	Micr. diagn.	Treatment prior to measurements		Mean value of 10—15 readings, millivolts
				Radium	Roentgen	
1	51	Stilbestrol bleeding	Endometrial atrophy ...	—	—	— 27
2	58	» »	—	—	—	— 25
3	48	Cerv. carc. III	Solid c.	—	1	— 10
4	30	Cerv. carc. I	Solid, squamous cell carc.	—	1	+ 11
5	50	Cerv. carc. III	Solid c.	—	1	— 23
6	66	Cerv. carc. III	Solid c.	—	—	+ 20
7	43	Cerv. carc. I	Adenocarc.	—	—	+ 4
8	28	Cerv. carc. I	Solid c.	—	2	+ 15
9	64	Cerv. carc. III	Solid c.	—	4	+ 23
10	62	Carc. of uter. corpus with with vag. metast.....	Adenocarc.	—	—	— 18
11	60	Cerv. carc. III	Solid c.	—	—	— 22
12	47	Carc. of uter. corp. and cerv.	Solid c. and adenocarc..	—	—	— 15

Case No.	Age	Clinical diagnosis	Micr. diagn.	Treatment prior to measurements		Mean value of 10—15 readings, millivolts
				Radium	Roentgen	
13	50	Carc. of uter. corp.	Adenopapil. c.	—	—	+ 24
14	57	Cerv. carc. I	Solid c.	—	—	+ 19
15	54	Cerv. carc. III	Solid prickle-cell carc. .	—	—	+ 31
16	38	Cerv. carc.	Solid basal-cell carc. ...	—	—	— 33
17	40	Cerv. carc. I—II	Solid c.	—	12	— 13
18	42	Carc. of uter. corp.	Adenocarc.	—	—	— 25
19	62	Ovarian carc. ascites...	Tumor cells	—	—	+ 20
20	60	Cerv. carc. I	Papillifer. adenocarc....	—	—	+ 25
21	66	Cerv. carc. III	Solid c.	—	—	+ 20
22	45	Cerv. carc.	Solid c.	—	—	— 33
23	50	Cerv. carc. IV	Solid c.	—	—	+ 12
24	40	Cerv. carc. I	Solid c.	—	—	+ 12
25	38	Cerv. carc. I	Solid c.	—	—	+ 32
26	67	Cerv. carc.	Solid basal-cell carc. ...	—	—	+ 18
27	66	Carc. of uter. corp.	Adenocarc.	—	—	+ 17
28	67	Cerv. carc. I	Solid c.	—	—	+ 29
(29	69	Cerv. carc. I	Probably solid c.	—	—	+ 32)
30	48	Cerv. carc. III	Solid c.	—	—	+ 40
31		Cerv. carc. I	Solid c.	—	—	+ 15
32	51	Cerv. carc. I	Solid c.	—	—	+ 60
33	65	Cerv. carc. I	Solid c.	—	—	+ 18

Among these 30 cases, it is seen that 9 (30 %) showed negativity and 21 (70 %) positivity of cervix. Two patients in whom carcinoma was not demonstrable, showed a negative potential.

The studies did not confirm LANGMAN and BURR's finding that a malignant tumor in the uterus was accompanied by a negative potential in nearly 100 %.

Discussion

The electromotive force measured between the two electrodes is the resultant of numerous single potentials. In living animal membranes, the electric potential is usually of the order of magnitude of 10—100 millivolts and the current density is very slight. The gastric mucosa, for instance, shows a potential of 10—50 mv. varying with the functional state of the mucosa. The skin also possesses a well-defined potential. Numerous reports have been published of measurements of potentials in isolated frog-skin, and recently USSING (5) demonstrated an intimate relationship between sodium ion transport in frog-skin and the potential difference between the inside and the outside of the skin. It is presumed that the site of active ion transport *i. e.* the site where the potential difference arises in this case is the stratum germinativum. Generally, the membrane potentials give rise to measurable potential differences between different parts of the body surface.

No doubt a malignant tumor is able to produce a change in these potentials, but it is not known whether such changes always go to the same side. Studying mammary carcinoma in the mouse, BURR (6) found a statistically significant alteration in the potential, but the changes were not sufficiently uniform to have any diagnostic value.

In connection with the measurements carried out by the authors, there is reason to point out some possible causes of potential variations which in our opinion exclude the possibility of obtaining results of a uniformity allowing of diagnostic application of such measurements:

(1) An ulceration, be it due to inflammation, malignancy or any other cause will doubtless give rise to an alteration in the potential.

(2) Changes in the potentials of unrelated organs situated between the electrodes (skin, bladder, parts of the intestine) influence the measurements.

(3) Several workers (7, 8) have proved that ovulation causes a pronounced, but rather brief alteration in the abdomino-vaginal potential.

SUMMARY

The bioelectric potential difference between the uterine cervix and the abdominal skin above the symphysis pubis has been measured in 30 cases of uterine carcinoma. Only 30 per cent. of the patients showed a negative potential of the cervix. This is in contrast with the findings of other workers who have reported negativity in about 100 per cent. of the cases and have therefore attributed diagnostic significance to these measurements.

Some factors which may influence the potential are discussed.

ZUSAMMENFASSUNG

Die bioelektrische Potential-Differenz zwischen der Cervix uteri und der Haut des Abdomens oberhalb der Symphyse wurde in 30 Fällen von Uterus-Carcinom gemessen. Nur 30 Prozent der Fälle zeigten ein negatives Potential an der Cervix. Das steht in Widerspruch zu den Ergebnissen anderer Untersucher die über ein negatives Potential in nahezu 100 Prozent der Fälle berichten und aus diesem Grunde dieser Messung den Wert eines diagnostischen Kennzeichens zuerkennen.

Einige Faktoren, die von Einfluss auf das Potential sein könnten, werden besprochen.

RÉSUMÉ

La différence de potentiel bicélectrique entre le col de l'utérus et la peau de l'abdomen au-dessus de la symphyse a été mesurée dans 30 cas de cancer de la matrice. Trente pour cent, seulement, des malades présentaient un potentiel négatif du col. Ces constatations s'opposent à celles d'autres auteurs qui ont signalé un potentiel négatif dans environ 100 % des cas et ont, de ce fait, accordé une valeur diagnostique à ces mesures.

Discussion du rôle de quelques facteurs pouvant influencer le potentiel.

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FROM THE SURGICAL DEPARTMENT (DIRECTOR: MED. DR. NILS LIEDBERG) AND THE ROENTGEN DEPARTMENT (DIRECTOR: DR. STIG BERGLUND), LASARETTET, EKSJÖ, SWEDEN

THE DISTRIBUTION OF GAS IN THE INTESTINE FOLLOWING LAPAROTOMIES UNACCOMPANIED BY COMPLICATIONS[1]

by

Nils Liedberg and *Stig Berglund*

Nowadays the collaboration between surgeons and radiologists ranges wide. This does not apply merely to routine diagnosis, but also to control during operation, such as *e. g.* in biliary and urinary surgery. Within bone and joint surgery, intimate contact between surgeon and radiologist is of the utmost importance, and in cases of approaching or possible postoperative complications, roentgen often affords valuable information. There are, however, still some gaps in this recent collaboration between surgery and radiology. One such gap represents a matter of the utmost importance and of daily occurrence, *i. e.* the roentgen appearance of the digestive canal following laparotomies unaccompanied by complications. Experience within this field is meagre. In other words: We lack sufficient knowledge of the, so to speak, »normal material» without which there are small chances of estimating where »normal» ends and »abnormal» begins.

Every laparotomy is followed by a more or less pronounced inhibition of the normal passage through and metabolism of the intestine. This leads to subjectively perceptible and clinically demonstrable postoperative meteorism which usually subsides within one or a few days.

It does not fall within the scope of the present paper to deal with the patho-physiological aspect of this postoperative gaseous distention which is influenced by numerous endogenous and exogenous factors. It must, however, be pointed out that in the series to be reported below, an adequate water balance was presupposed and controlled. Furthermore, early rising after the operation was practised as a routine prophy-

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laxis against thrombosis. Among other factors of significance in this respect, it is not out of place to mention here that different anaesthetic methods will indeed influence the postoperative course in this respect. Regrettably, the present small series affords no basis for an evaluation of this problem.

Our roentgen studies were designed to afford an idea of and preferably also a certain standard by which to judge the degree of the retarded passage through the digestive canal. At the outset, we thought that ordinary roentgen examination of the passage by means of a barium meal before and immediately after laparotomy would supply the answer to our question. In a case of uncomplicated cholelithiasis, the passage through the small intestine before the operation took between 2 and 3 hours from ingestion of the opaque medium until it reached the colon. Eight hours after the ingestion, all the barium was in the colon. Twenty-four hours after cholecystectomy — performed under spinal anaesthesia by the method of Sebrechts — the same patient was again given a barium meal. This time, the opaque medium remained in the stomach for more than 48 hours, before it began its downward passage which took 68 hours before all the contrast had reached the colon. A more detailed evaluation of the time could not be made, since the stomach emptied in several stages. In another case, the opaque medium was retained in the stomach for the same length of time, but when once the stomach had started emptying, all the barium had reached the colon in 26 hours.

These postoperative studies gave a positive result in so far as they illustrated partly the pronounced reduction in gastric motility — at least as far as fluids are concerned — which may occur during the first days after laparotomy, partly a marked retardation of the passage through the small intestine.

An observation of even more importance was that in spite of the retention of the entire opaque meal in the stomach 48 hours after the operation, the downward passage of gas from the stomach appeared to take place unhindered. This is clearly illustrated by Fig. 1 showing the roentgen appearances 72 hours after cholecystectomy, where the entire opaque meal is still in the stomach 2 days after ingestion, whereas gas is seen in the duodenum as well as in several coils of the small intestine.

In the subsequent cases, we abandoned the barium meal and adopted instead the procedure of studying the postoperative appearances by means of the so to speak spontaneous content of the intestine after operation, *i. e.* the intestinal gas. The studies were confined to a daily survey of the abdomen, partly in the supine position and partly in the lateral horizontal positions.

The gaseous content of the intestine in so-called paralytic ileus has been studied by numerous workers, in Sweden *inter alia* by OLIVECRONA

and WAHREN. According to WANGENSTEEN (1942), the gaseous content in an obstructed intestine may be up to 68 per cent., depending on and due to swallowed air. The remaining 32 per cent. is formed in the body, two-thirds by diffusion of blood gases, whereas one-third is formed within the intestinal lumen. According to MAGNUSSON (1931), a lively and brisk passage of swallowed air is taking place normally from the stomach down through the small intestine. The rate of this passage, the undisturbed and normal metabolism in the bowel, and the fact that the gas is probably distributed into small bubbles explain why this gas is not normally visualized on the roentgen film of the small intestine. Normally, roentgen shows gas only in the stomach and to a certain extent also in the colon, but it is only in exceptional cases that an occasional bubble of gas is visualized in the small intestine, and, if so, usually in the duodenum. In case, however, the passage through the small intestine is inhibited, retarded, or arrested, be the cause mechanical or adynamic, which latter group includes *inter alia* the postoperative inhibition under discussion, the gases accumulate and occupy a small or large proportion of the small intestine.

Fig. 1. The entire barium meal in the stomach, whereas the gas has passed down into the small intestine.

The object of the present study was, therefore, to try to elucidate what can be designated as the »normal postoperative condition» of the intestine by the aid of the inevitable disturbance of the gaseous passage in the intestinal canal as illustrated by the clinical picture in each individual case.

The series comprises 50 patients who underwent laparotomies and whose clinical postoperative course was uneventful:

7 gastric operations
14 operations on the biliary tract
17 appendectomies
6 gynaecological laparotomies
3 operations on the colon
2 herniotomies and
1 exploratory laparotomy.

Fig. 2.

Fig. 3.

Fig. 4.

Figs. 2, 3 and 4. One, three, and seven days after cholecystectomy.

It is distinctly apparent from the observations, as was also expected, that accumulation of gas in the small intestine is considerably less marked and more rarely demonstrable following comparatively brief interventions, such as easy appendectomies, than following *e. g.* operations on the biliary tract or gastric interventions. Among 17 appendectomies carried out under ether anaesthesia, unmistakable accumulation of gas was visualized in the small intestine of only two. This does not mean, however, that the roentgenograms of the remaining 15 did not show any gas at all in the small intestine. Slight amounts of gas in the intestinal canal were seen also in these cases, but confluent gas, localized with certainty in the small intestine, was not recorded. In this connection it must be pointed out that, according to

Fig. 5.

Fig. 6.

Fig. 7.

Figs. 5, 6 and 7. One, two, and four days after gastrectomy.

Koch *inter alia*, patients with acute appendicitis usually exhibit moderate accumulation of gas in the intestine before the operation, even as early as within 24 hours of the onset of the attack. Such gas is, however, preferably confined to the colon.

Whereas marked accumulation of gas in the small intestine was found in only two of 17 cases of uncomplicated appendectomies, the appearance was a different one in the case of uncomplicated operations on the biliary tract and gastrectomies. Following 20 such interventions — carried out under spinal anaesthesia by the method of Sebrechts — 16, or no less than four-fifths of all the subjects, exhibited large amounts of gas in the small intestine during the immediate post-operative days. As early as 24 hours after these interventions, there is usually a pronounced distention of several coils of the small intestine.

Fig. 8. Fig. 9.

Figs. 8 and 9. The stomach 24 hours after gastrectomy and three days later after having been drained in the meantime.

In the course of the subsequent 24 hours, this gaseous distention in the small intestine appears to increase and thereupon decrease in order to manifest itself in large parts of the colon. Four days after the operation, roentgen usually fails to record pronounced content of gas in the small intestine.

These observations are clearly illustrated partly by Figs. 2, 3, and 4 showing the postoperative appearances after uncomplicated cholecystectomy one, three, and seven days respectively after the operation, partly by Figs. 5, 6 and 7 showing the appearances one, two, and four days respectively after gastrectomy (Billroth II) for duodenal ulcer.

It is striking and worth emphasizing that in this series of clinically uncomplicated abdominal operations, roentgen *did not in any case demonstrate fluid levels*, not even in the presence of comparatively pronounced gaseous distention of the coils of the small intestine. Therefore, there is perhaps reason to presume that a finding of such fluid levels on a postoperative roentgenogram would justify a suspicion or even constitute a warning of an existent or approaching postoperative complication and thus become of the greatest value in the individual case.

There is a factor in connection with these roentgen examinations following gastrectomy (all by Billroth II and retrocolic high gastroenterostomy) which may be worthy of note. As early as 24 hours after the operation, there is marked distention of the gastric stump (Fig. 8),

and, moreover, the gas may be seen passing through the (oedematous?) stoma down into the small intestine. This is better illustrated by Fig. 9 showing the appearance in the same case 4 days after the operation, when the considerably less distended gastric stump has been drained through a duodenal tube — a routine procedure during the first postoperative days.

Our roentgenographic studies of the postoperative course of clinically uncomplicated abdominal operations, therefore, appear to show that accumulation of gas in the small intestine is a comparatively rare occurrence and usually slight following brief uncomplicated laparotomies, such as appendectomies. In cases of more considerable and more prolonged intra-abdominal interventions, however, such as operations on the biliary tract or the stomach, there is usually an extraordinarily pronounced gaseous distention of major or minor parts of the small intestine. As a rule such distention persists until about the 4th postoperative day and probably indicates retarded passage and absorption of swallowed air. The increased gaseous content of the colon three to four days after the operation also fits in with the presumption that the rate of gaseous passage begins to increase at this juncture. The absence of any fluid levels in the distended small intestine is probably interpretable as a sign of the benign nature of the gaseous distention.

SUMMARY

Postoperative roentgen studies in 50 cases of clinically uncomplicated laparotomies have shown considerable gaseous distention of the small intestine during the first four days after at any rate the major interventions (upon *e.g.* the biliary tract or the stomach). This gaseous distention is presumed to be due to retarded passage through the intestine and absorption of swallowed air. Its benign nature appears to be borne out by the absence of fluid levels in the small intestine.

ZUSAMMENFASSUNG

Postoperativ vorgenommene röntgenologische Untersuchungen in 50 Fällen von klinisch unkomplizierter Laparotomie haben eine beträchtliche meteoristische Erweiterung im Dünndarm während der ersten 4 Tage ergeben, jedenfalls nach den grösseren Eingriffen (so z. B. am Gallengang-System und am Magen). Es wird angenommen, dass diese Gas-Aufblähung durch die Verzögerung der Darmpassage und der Absorption der verschluckten Luft hervorgerufen wird. Ihre gutartige Natur gibt sich durch das Fehlen von Flüssigkeitsspiegeln in diesen Dünndarmschlingen zu erkennen.

RÉSUMÉ

L'étude radiologique postopératoire de 50 cas de laparotomies sans complications cliniques a montré une distension gazeuse considérable de l'intestin grêle pendant les premiers quatre jours, cela du moins après des interventions majeures (par ex. sur les

voies biliaires ou l'estomac). On présume que cette distension gazeuse est due à un retard du transit intestinal et de l'absorption d'air dégluti. Sa bénignité ressort de l'absence de niveaux hydro-aériques dans l'intestin grêle.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR: DR. LARS LÖNNERBLAD) OF THE PROVINCIAL HOSPITAL, VÄSTERVIK, SWEDEN

THE VALUE OF A TOTAL POPULATION ROENTGEN CHEST SURVEY IN THE CAMPAIGN AGAINST TUBERCULOSIS[1]

by

Lars Lönnerblad

Introduction

In discussing the various measures used to combat tuberculosis, it would seem as though the results of recent research have been disregarded to a certain extent. We have in mind particularly *the known high incidence of tuberculous infection* in the general population, *the difficulties of giving a prognosis* and, finally, *the apparent, rather poor results of therapy*, even in the early stages of pulmonary tuberculosis. Naturally, these factors decisively *influence the chances of successfully isolating infectious persons* and therefore of protecting non-infected persons from exposure. In the words of HOLM (1948), »No home is safe from tuberculosis until every home is safe».

Under existing conditions, it would probably be necessary to intervene before the infection has taken place and thus accomplish what is done against other very frequently epidemic or endemic diseases: i. e. *perform mass inoculation* in order to reduce the incidence of T.B.C. and thus avert the problems which naturally result.

It is not my purpose to deal at length with the histogenesis and classification of pulmonary tuberculosis although these are admittedly relevant factors. I shall confine the discussion to the basic features outlined above. By and large our point of view has not changed appreciably from that expressed in 1942 at the 23rd Swedish Medical Congress and at the Convocation of Swedish Phthisiologists the same year. At that time we

[1] Briefly presented at the 16th Meeting of the Northern Association for Medical Radiology, Stockholm, June 10—12 1949; submitted for publication May 29, 1950.

based our conclusions on a relatively small series of cases, but during the intervening years we have assembled and followed up a larger series, so that we now feel justified in again recording our opinions relative to this matter.

The Incidence of Tuberculous Infection in the Population

On the basis of a series comprising more than 11,500 persons, all of whom had been subjected to the Mantoux test (1 mg), GUNNAR DAHLBERG obtained the curve reproduced in fig. 1 showing the susceptibility to tuberculin at various ages of the Swedish population. Judging from

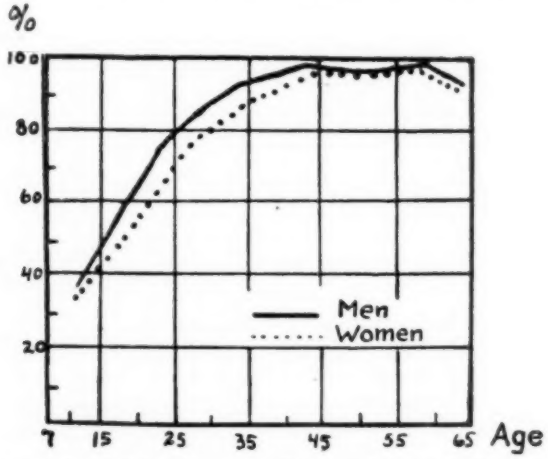

Fig. 1. Percentage of Swedish Tuberculin Positive Men and Women at various Ages. (Courtesy of DAHLBERG.)

this curve, the frequency of positive reactions to tuberculin increases comparatively quickly from the beginning of the school age to the age of 25 or thereabouts. Thereafter the curve rises more slowly and it does not attain its maximum until the age of 40 to 45, at which time 98 per cent of the population are shown to be positive to tuberculin.

Practically speaking, therefore, every individual in Sweden sooner or later becomes positive to tuberculin, and similar figures are available for other countries (ANDENAES, JOHS. and MOGENS HOLM).

DAHLBERG gave no detailed discussion of the implications of this high incidence of tuberculin positive individuals, but in the majority of instances it may be assumed that it is a sign of a tuberculous infection either active or static.

Some Comments on Tuberculin Tests

Even though the positive tuberculin test may be a sign of tuberculous infection, it seems as though tuberculin tests sometimes have been accorded too much significance. For example, SEMB wrote: »Die Tuberculinreaktion zeigt an, ob der Organismus mit Tuberkulose infiziert ist oder nicht. Sie ist als notwendige Voraussetzung der Diagnose: Tuberkulose anzusehen.» Admittedly, he added somewhat later in his paper: »Bei sicher negativem Ausfall der Reaktion darf im allgemeinen davon ausgegangen werden, dass der Untersuchte keine Tuberkulose haben dürfte.» He might have emphasized, however, that active tuberculosis may be present, although a properly executed tuberculin test is negative. HEDVALL published 4 cases in which active pulmonary tuberculosis with bacteria pathogenic to guinea pigs was present, despite negative tuberculin reactions: there were no complicating diseases present which might have reduced the susceptibility to tuberculin and the physical condition of the patients was good. Others have reported similar findings.

As long ago as 1927, in a discussion of the pathogenesis of scrofuloderma, LAURELL strongly emphasized that the allergy to tuberculin, which is characteristic of many scrofulous patients, needs not necessarily be due to tuberculous infection. This fact has been demonstrated in experimental studies by SELTER and TANCRÉ.

HELLERSTRÖM has pointed out that the tuberculin reaction is no more specific than any other biologic reaction can be expected to be; and that an allergic condition must not be regarded as a stable condition but that positive and negative phases probably exist. His view is borne out by SEEBERG's investigations.

Some experiences gained from tuberculin reactions and immunity tests support the view that immunogen and allergen are different substances (CALMETTE, WIDSTRÖM). Judging by the literature, it would seem this point sometimes has been overlooked as well as the fact that in all probability there exists both specific and non-specific immunity to tuberculosis.

As emphasized by LAURELL (1937) in a paper on predisposition to tuberculosis of the upper portions of the lungs, particularly in orthostatic arterial anemia, it is conceivable that a strong allergy to tubercle bacilli may even *promote* the development of a tuberculous process.

In studies on »skin tuberculosis» in cattle (»skin lesions in tuberculin reacting cattle»), HEDSTRÖM and others were of the opinion that they could exclude the possibility that the lesions were caused by tubercle bacilli of the human, bovine or avian type; despite the facts that the animals showed allergy to tuberculin, and that the granulomata exhibited a tubercle-like structure (colliquative necrosis and calcification, as well as alcohol-acid-fast micro-organisms; which, however, were not pathogenic to guinea pigs). GELLERSTEDT has found seven instances of similar changes in man, although, as he wrote, »closer classification of the etiology cannot be attempted before positive culture and animal tests have been made». (In GELLERSTEDT's cases it has unfortunately been impossible to clarify exactly the data relative to the tuberculin reaction.)

In this connection it perhaps should be stressed that the bacteria ought to be proved pathogenic to guinea pigs. Unless this is the case, too frequent diagnoses of tuberculosis is likely. It goes without saying that a diagnosis so important as tuberculosis should not be made without legitimate reasons.

Eventually some tuberculin positive persons surely become negative again. The time of infection seems to a large extent to have shifted from childhood and youth to a more mature age, possibly in part because bovine tuberculosis (milk infection), has been for the most part eliminated by that time.

Undoubtedly, however, numerous human carriers of tuberculosis are at large. It may be added that these are cases of *both known and unknown active »open» tuberculosis.*

The Possibilities of Isolating Carriers of Tuberculosis

There are two outstanding reasons why it is impossible to isolate all tuberculous individuals effectively.

1. The disease is usually insidious in onset and of *long duration* and does not always entail complete or even partial inability to work. Such patients cannot, therefore, be detained indefinitely in sanatorium.

2. Pulmonary tuberculosis may take the form of a *rapidly progressing process* that suddenly erupts in a lung which a short time before had been considered healthy; or as a sudden re-activation in a lung which had been observed for a long time with presumably inactive changes.

Ad 1. Cases of the first type are so common that it may seem superfluous to give any examples. I shall therefore only briefly cite the case of a comparatively *young* man with extensive, relatively static pulmonary changes. In all probability his lung process was »open» from time to time, particularly during periods of a superimposed non-specific upper respiratory infection.

T. F., born 1915, stone-mason. Fluoroscopy in November 1943 revealed fairly numerous, ill defined infiltrations in the upper part of both lungs down to the level of the anterior third costal arch.

He was treated at a sanatorium from 8/3—20/6 1944 and was afebrile all the time. The sedimentation rate was 5—7 mm per hour. Eight antiformin tests were negative, but a bacterial culture of a stomach lavage 16/5 1944 showed tubercle bacilli. The sputum examination made after his discharge from the sanatorium on 10/3 1945 was negative.

After being discharged from the sanatorium, the patient has been at work all the time and has felt well, apart from brief periods of coughing.

The changes chiefly in the lateral right first intercostal space and the lateral left second intercostal space did not remain quite stationary, but on the whole the roentgenographic picture was relatively static.

In a brother, two years younger, B. F., infiltrations were simultaneously discovered which clinically and roentgenographically were of the same type as those in the brother, T. F., but no tubercle bacilli could be demonstrated in the younger brother.

Since in the adult it often takes months and years before the disease becomes clinically or roentgenographically manifest, it is in many cases impossible to trace the source of the tuberculous infection and to know which persons have been infected by any given carrier. It is indeed difficult enough to determine these facts in dealing with infectious diseases with an incubation period of only a week or two.

It is not to be considered unusual that some cases of »open» tuberculosis are found when an industrial plant with hundreds of employees is surveyed. Each individual case, however, must be carefully investigated

Patient T. F., born 1915

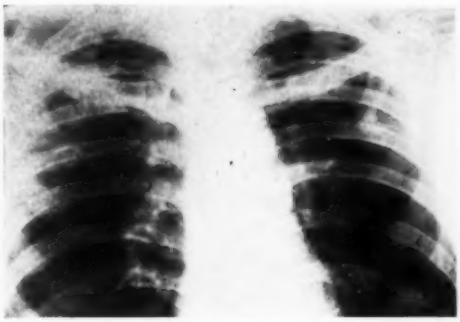

Fig. 2a. Roentgenograph 19/4/1944 showing numerous, partly ill defined infiltrations in the upper part of the lungs down to the level of the anterior third costal arch.

Fig. 2 b. Roentgenograph 1/4/1949 on the whole visualizing an unchanged condition.

to ascertain whether the diseased person actually has been infected at the place of work.

It seems to us that some persons with proved or unproved tuberculosis may not necessarily act as carriers, whereas others with rapidly progressing tuberculosis (irrespective of whether the process involves a lung recently thought to be healthy or one superimposed on an old static process), in a short time can be a source of infection to a large number of persons.

Because of economic stress, it is probable that many tuberculous persons with trivial infections of the respiratory passages — a complication to be considered most dangerous in pulmonary tuberculosis — try to keep on working as long as possible for the sake of the wages. It is often that the diseased person dares not hold his handkerchief to the nose and mouth when he coughs, because he fears that his condition will be suspected: and thus the fear of infection among the public is created. In this respect the intensive propaganda to track down disease carriers has turned out to be a double-edged sword. By stressing the importance of eliminating sources of infection — although this is not and cannot be accomplished to an adequate extent — one still further handicaps the sufferer from tuberculosis in his search for work and other means of improving his economic status, after discharge from the sanatorium. Both employers and employees look askance at persons with tuberculosis at work, and the latter therefore have difficulties in obtaining the nourishing food and good housing that they were told to arrange for after leaving the sanatorium.

Patient E. G., born 1907

Fig. 3 a. Photofluorograph 2/5/1947 reveals a small shadow rather medially in each second intercostal space, perhaps artefacts.

Fig. 3 b. Roentgenograph 7/11/1948 illustrates clouding and a soft infiltration with cavitation in the upper half of the left lung.

Ad 2. Tuberculosis may, on the other hand, manifest itself as a *rapidly progressing process*, coming *unexpectedly*.

E. G., born 1917, factory worker. Negative Mantoux (1 mg) at place of work 1945. Photofluorographed 1947 because a brother had contracted tuberculosis. The appearance of the lung seemed normal. Later re-examination revealed a slight haze (perhaps artefacts) in the medial portion of each second interspace (fig. 3 a).

In August 1948 the patient developed a severe cough with expectoration and nocturnal sweating; he felt tired. On November 7th 1948, he visited a physician who sent him for a roentgen examination, which revealed clouding and a soft infiltration with cavitation in the upper half of the left lung (fig. 3 b). An antiformin test was positive. Pneumothorax treatment was considered ineffective and after treatment with PAS (paraaminosalicylic acid) superior thoracoplasty was performed 15/11 1949. Postoperatively, the temperature rose and there was circulatory insufficiency. The patient died 21/11 1949.

K. L., born 1922, unskilled labourer. Photofluorographed March 16, 1949. Some soft infiltrations were visualized in the right supraclavicular region (fig. 4 a).

Roentgenography 13/6 1949 (fig. 4 b) revealed scattered, cloudy infiltrations in most of the right lung, the changes being less marked towards the base. At the apex there was a cavity about as large as a walnut, containing air. The first and second left intercostal spaces contained a few small cloudy infiltrations. Tubercle bacilli were found in the sputum.

Mrs. J.-L., born 1913, wife of telephone worker. Employed as laundress and assistant nurse at sanatorium 1933—1936.

Roentgenographic examination at the sanatorium 29/4 1936 (fig. 5 a) revealed small, ill defined infiltrations supraclavicularly at the apex of both lungs. The changes were interpreted as inactive.

Patient K. L., born 1922

Fig. 4 a. 16/3/1949: Photofluorograph demonstrates some soft infiltration in the right supraclavicular region.

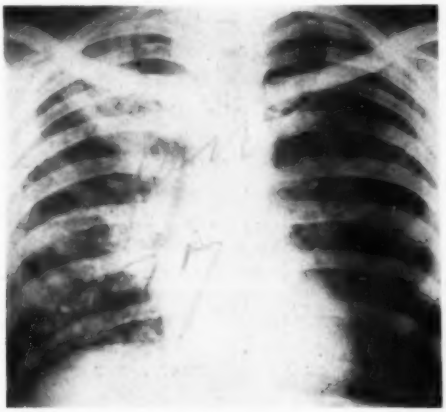

Fig. 4 b. 13/6/1949: Roentgenographic picture of scattered, cloudy infiltrations in most of the right lung and a cavity at the apex.

She was sent to the roentgen department of Västervik Hospital 13/7 1940, because she had been coughing for some months. The roentgenographic examination (fig. 5 b) showed some regressive change at the apex of both lungs but no marked deviation from the picture of 1936. A later check-up was suggested. Re-examination 14/8 1940 showed that the condition was about the same as a month earlier. Her lungs were fluoroscoped in July 1941 by another physician who observed no pathologic changes. On 18/8 1941 she was admitted to Västervik Hospital for symptoms of polyarthritis. Pulmonary roentgenography 19/8 1941 (fig. 5 c) revealed numerous infiltrations decreasing towards the base in the upper two-thirds of the left lung, and cavities at the level of the clavicle. The sputum contained tubercle bacilli.

The patient was transferred to a sanatorium where pneumothorax was instituted on the left side. With increasing infiltration of the *right lung* the patient died 14/9 1943.

Mrs. Ada B., born 1885, wife of business man, reportedly had something »wrong with one lung» at age 11. She has been examined many times through the years, most recently in December 1940 (fig. 6 a). At this time only small pulmonary changes that apparently had healed were observed in the apex of the left lung.

The patient was admitted to Västervik Hospital January 9th 1942 for gastric roentgenography. A routine fluoroscopic examination of the lungs visualized fairly extensive infiltration in the right lung and a tangerine-sized cavity located laterally and posteriorly immediately above the hilum (fig. 6 b and 6 c).

The sputum contained many acid-fast bacilli. The lesion progressed despite sanatorium care and the patient died June 15th, 1942.

Previous examinations in both these cases may easily have given the patient a false sense of security, putting him in a less desirable position than if he had not been examined at all, and probably allowing him to infect hundreds of persons before the diagnosis was made.

Patient J.-L., born 1913

Fig. 5 a.

Fig. 5 b.

Fig. 5 c.

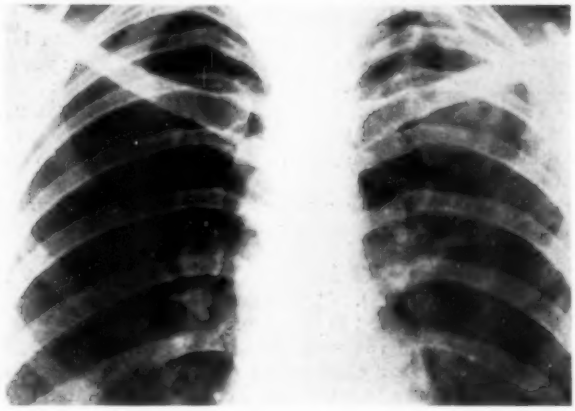

Fig. 5 a. Roentgenograph 29/4/1936 shows small, ill defined infiltrations supraclavicularly at the apex of both lungs.

Fig. 5 b. Roentgenograph 13/7/1940 shows some regressive change at the apex of both lungs.

Fig. 5 c. Roentgenograph 19/8/1941 shows numerous infiltrations, decreasing towards the base and cavities at the level of the clavicle.

Patient Ada B., born 1885.

Fig. 6 a.

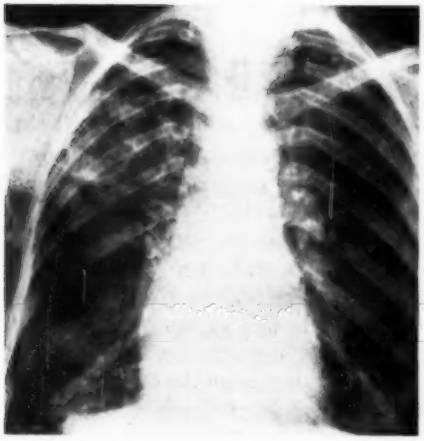

Fig. 6 b.

Fig. 6 c.

Fig. 6 a. Roentgenograph 20/12/1940 demonstrating small changes at the apex of the left lung.

Fig. 6 b, c. Roentgenographs 9/1/1942 demonstrate fairly extensive infiltrations in the right lung and a tangerine-sized cavity located laterally and posteriorly immediately above the hilum.

The Difficulties of Making a Prognosis of Tuberculous Pulmonary Changes and Their Consequences

The difficulty of predicting the outcome of pulmonary changes has been emphasized by MALMROS and HEDVALL, etc. These writers point out what they recognize as the subprimary, initial foci, often determined only after a very long period of observation that may require decades.

Similar experiences have recently been published by Dr. JOHN LUNDQVIST, M. D., the Secretary of the National Swedish Association against Tuberculosis. He expressed the opinion that *not for about 30 years would there be any appreciable decrease of the mortality in tuberculosis, even if there were not a single new infection:* so many of those already infected would successively fall ill and die.

LUNDQVIST's statement emphasizes the difficulty of evaluating large-scale countermeasures against tuberculosis. However, his opinion seems far too pessimistic, if, for no other reason than that the mortality from tuberculosis near age 25 is relatively high and that all deaths below that age would be eliminated. Furthermore, the mortality during the *first few* years after infection with tuberculosis probably is rather high.

Obviously, owing to the dissimilarity between tuberculosis and most other infectious diseases, it is impossible to obtain reliable statistics as to the number of clinical as well as of the number of »open» cases of tuberculosis. The official Swedish statistical yearbook for 1947 (published in Stockholm 1949, p. 53) stated: »At the end of 1947, 89,043 persons had tuberculous disease. Most of them, or 59,076, had pulmonary tuberculosis, but only 8,990 in the infectious stage (»open» tuberculosis). *It is often difficult to determine whether the tuberculosis is in the infectious stage; consequently, these figures should not be regarded as representing the exact number.*» (Italics are mine.)

As far as tuberculosis is concerned, the population cannot be classified — as sometimes is attempted — under the simple headings »healthy» and »diseased», just as is done in most other infectious diseases such as scarlet fever. This fact is indirectly implied in the statement by LUNDQVIST quoted above. Actually, there is a large group to be taken into account, that includes all infected persons who are not considered definitely tuberculous, because of the atypical manifestations described above.

Mass examinations have given us some idea of how common small tuberculous foci really are. A study, published by MEDLAR, of 1,225 *necropsies* on adults in cases of sudden and unexpected death seems to be highly significant because of his findings in the lung material. He demonstrated »minimal pulmonary tuberculosis» in 96 persons out of the above series, and the disease was completely healed in only 13 of them. One of the conclusions drawn by MEDLAR from his study is the

following: »Shadows caused by tuberculous lesions in the upper lung fields should not be interpreted as 'healed' if there are scattered small calcific densities, for the majority of such lesions also contain unorganized necrotic (caseous) areas of tuberculous pneumonia.»

As indicated in the foregoing, it has been shown that in many countries, practically the whole population is exposed to tuberculosis. The majority of persons themselves overcome the infection and in some cases even extensive pulmonary lesions may heal spontaneously. It is not known, however, just what it is that in a relatively small number of persons causes *clinical tuberculosis* with high mortality despite all therapeutic measures, the mortality in cases of »open» tuberculosis being equivalent to that in cases of malignant tumours. The development of the disease often seems to be independent of any definite therapeutic procedure. Although the patient often comes under care long before he has developed any discernible pulmonary infiltrations, as in the cases of tuberculous pleurisy and in the form of erythema nodosum associated with tuberculosis (cf. LÖFGREN for differential diagnosis), it has been impossible to demonstrate any positive results of treatment. Within a few years most such patients have progressive tuberculosis, and according to various authors the mortality approaches 10 per cent.

It would consequently seem as though the fact that cases of pulmonary tuberculosis are diagnosed »in time» must not be accorded overdue therapeutic importance. It is probably true that the expressions »the patient is under observation» may be frankly dangerous, because it may lull the people concerned into a false sense of security. When so-called progressive tuberculosis has set in, it may already be too late to do anything about the situation, for once it has started, such a process goes on unhampered.

In this connection, we particularly wish to emphasize that even regression of the pulmonary lesions is not always a favourable prognostic sign. Sometimes regression may be merely a sign that the process is not stationary; and a regression is rather frequently followed by even stronger *progression*.[1]

It seems perfectly obvious that social conditions are of the highest importance. In large statistical studies from England and other countries (e. g. HART and WRIGHT) a comparatively high mortality in tuberculosis has been found in the lower social strata, e. g. in the class of unskilled workers. Experiences gained during both World Wars (FABER, HOLM) suggest the same thing, viz. that the greatest number of people with active tuberculosis is found among those who live under cramped housing

[1] For the purposes of comparison, it would be most valuable if photofluorographs were properly indexed. Sometimes, however, this practical detail seems to be rather unsatisfactorily carried out.

conditions, unfavourable hygienic circumstances and qualitative and quantitative undernourishment. These findings seem to be confirmed by FORSGREN's sociologic-hygienic studies of school-children.

In the long run, however, the constitutional element seems to be the deciding factor (KALLMAN and REISNER). By process of elimination, persons comparatively susceptible to tuberculosis die relatively early in life and therefore have had less time to procreate than the rest of the population; thus a selection effect should be noted.

DAHLBERG has emphasized that less inbreeding due to improved communications and travel might have a bearing on the matter.

The Results of Pulmonary Tuberculosis Treatment

As emphasized by PINNER and others, the evaluation of results of treatment of pulmonary tuberculosis is an extremely complicated and essentially unsolved problem.

PINNER has pointed out some of the most obvious difficulties: »The chronicity of the disease introduces the question of the minimum length of observation time necessary to reach valid conclusions; if it is too short, the whole story of the disease process is not encompassed; if it is too long, the effect of treatment may become obscured by complications, either of a tuberculous nature . . . or by non-tuberculous disease . . . Furthermore, since living conditions in all their general and some quite specific aspects play such an important rôle in the course of the disease they will frequently, in one or the other direction, over-shadow the direct results of the treatment that was given several years before a final judgement can be rendered.»

PINNER pointed out further »the number of the patients must be very large, usually larger than that observed by one physician or even one institution.» Like other authors he stressed the fallacy of comparing patients in the pre-collapse era with patients — say ten years later — who were treated by pneumothorax.

He stated that in his opinion the death rate in tuberculosis has dropped. Perhaps this is true also in regard to Sweden, at least in the sense that fewer persons die although »everybody» is infected.

The curve showing the mortality from tuberculosis for Sweden (fig. 7) drops fairly uniformly from about the turn of the century — *long before any medical countermeasures worthy of the name were initiated* — to the present time. The less reliable figures before 1900, from about 1880, show the same tendency.

Up to the second World War, the mortality in tuberculosis in many other countries showed a similar rate of fall (KAYNE, PAGEL and O'SHAUG-

Fig. 7. Mortality in Tuberculosis per 10,000 Inhabitants in Sweden.
Total annual tuberculosis death rate ————————
Annual death rate from consumption ----------

NESSY), except for a slight increase at the end of the first World War probably due to the shortage of certain foodstuffs at that time (FABER).

At least in Sweden, some cases of pulmonary tuberculosis that otherwise would have been classified as marasmus senilis or the like have been discovered and therefore correctly labelled in the official statistics. The number of such cases is not known with certainty; but it is to be supposed that the death rate perhaps would have dropped more sharply, had the hunt for persons with tuberculosis been less intensive.

PINNER reasoned that owing to various circumstances such as bilateral involvement, obliteration of the pleural space, etc., the final figure for the success pneumothorax is probably not higher than 12 to 15 per cent. Satisfactory results may be expected in well above 50 per cent of those in whom adequate treatment is possible. The breadth of indications, for example, must obviously be of great importance in this connection.

GUNNAR BERG compiled statistics, including practically all cases diagnosed during life of »open» pulmonary tuberculosis in the city of Gothenburg. These were assembled from 1910 to 1934 and comprised 6,156 subjects over the age of 15, of which 3,048 were men and 3,072 women. In the total series it was shown that 70 to 80 per cent of patients with »open» tuberculosis of the lungs die within 10 years.

In order to find the effect of collapse treatment, BERG determined the mortality of collapse-treated cases and of cases which were not subjected to such treatment. He stated that »treated and non-treated cases from the same period are not *a priori* comparable, as the non-treated cases constitute a selection and as very severe cases are included in this group». He pointed out that »we have to reckon with the fact that, in later periods, less severe cases were included to a somewhat larger extent. The difference obtained amounts to a decrease in mortality by 10—15 per cent of the mortality characterizing the non-treated cases. This is only an approximate figure for the effect of treatment.» »At any rate», BERG continued, »we may maintain that the effect of the treatment under no circumstances is very great. A rough estimate shows that collapse treatment cannot have been very important as a direct cause of the decreased general mortality from pulmonary tuberculosis (the decrease in mortality amounts to 50 per cent from the period 1910—1915 to 1930—1935.» (In Sweden.)

The same mortality of open tuberculosis as obtained by BERG, i. e. at least 70 per cent within 10 years, has previously been found by BRAEUNING and NEISEN and later by LASSEN.

No figures contradicting the above have to my knowledge been published; provided the statistical analysis has been satisfactory. As for chemotherapeutical and antibiotical substances, one has perhaps not yet had sufficient experience of these.

Even if it is true that housing and nutrition do not so greatly affect the prognosis as we are prone to believe, the aid extended to tuberculous persons in any event should be increased. It is by no means a simple matter for a person »on poor relief» to obtain adequate housing and food. He is simply forced to get himself a job of some sort to supplement his »poor relief».

Then there are of course many borderline cases, in which perhaps something really could be done by improvement of the social circumstances. We have in mind the estimated tens of thousands of cases in Sweden which may be of the subprimary, initial foci type, where progression possibly could be avoided thereby.

The Result of Mass Photofluorography on the Swedish Island of Gotland

Although the data from the photofluorography mass examination attempted on the entire population of Gotland made in 1943 has not yet been fully analyzed, it in a measure seems to confirm my hypotheses of 1942, viz. that a total population chest survey does not yield any conclusive results.

Of the data hitherto published from the Gotland survey, I should like, in the present connection, to mention the following:

Gotland would seem to be almost ideal for a successful campaign against tuberculosis. The island is comparatively remote and has a negligible immigration factor. It is 6—7 hours by sea from the mainland.

In the photofluorographic mass survey of 1943, altogether 56,964 persons were included which is equivalent to 99 per cent of the population over age 1 (according to NORDGREN). Consequently an unusually large percentage of the population participated in the survey, as compared with the average participation in similar surveys within and outside Sweden.

It appeared, nevertheless, that on Gotland the mortality in tuberculosis has not dropped (numerically speaking) quicker than in the remainder of Sweden, where photofluorographic surveys have as a rule not yet been undertaken.

The mortality in tuberculosis per 1,000 inhabitants was for:

Year	Gotland	Sweden as a whole
1942	0.96	0.68
1943	0.98	0.68
1944	0.64	0.65
1945	0.81	0.59
1946	0.54	0.51
1947	0.49	0.48
1948	0.70	0.48

As early as 3 years after this great regional survey, it was apparent that more than half the newly discovered cases of tertiary tuberculosis of the lungs already had passed the moderate stage.

In but one-fourth of the newly discovered patients over age 16, the source of infection was considered localized, by means of environment analysis etc.

With this in view, the statement is perhaps justified that *no appreciable results* were obtained from the point of view of the prevention of tuberculosis.

Discussion

Since carriers of infection apparently cannot be effectively isolated and our therapeutic resources seem to be comparatively small, it is not out of step to centre our attention on the improvement of the resistance of the entire population in a manner similar to that adopted for other very common infectious diseases, e. g. typhoid fever, etc.

From the foregoing discussion, it would seem that socio-medical countermeasures probably are very important. With the advent of BCG vaccination (perhaps the term »inoculation» should be used in place of »vaccination» since it involves living bacteria and is not a vaccine in the strict sense of the word), we have at our disposal an additional agency of considerable protective value (WALLGREN, ARONSON). The technique to be used and the duration of the protection in the individual case are still uncertain. However, as long as *everybody is in the danger zone* and is potentially a contact case, it is, to a certain extent, too late when the infection already has taken place. BCG vaccination should perhaps be employed on a scale many times larger than the present. Since in some cases the protection only lasts a few years, the number of inoculations per annum, after the population has been inoculated systematically, should perhaps constitute a multiple of the birth rate.

It is obvious that photofluoroscopy is very important whenever a large special group of persons have to be segregated in barracks or educational establishments, since carriers of tuberculous infection can be separated fairly effectively thereby.

Of course, we by no means wish to deny that photofluorography also can be of importance in certain other circumstances (one can of course sometimes also detect certain other intrathoracic diseases on the photofluorograph), but it is nevertheless a fact that examinations at intervals of 5 or 10 years reveal cases of early tuberculosis only at random. Many factors indicate that when a person has been infected with tuberculosis, it is a bit too late to do anything about it. Therefore since carriers of infection cannot be properly isolated, it seems justified and advisable to promote a means of general prophylaxis throughout the population. Such a means is available in BCG vaccination.

SUMMARY

The author points out that in his opinion there are many reasons why photofluorography of the entire population is not very likely to be very successful in combating tuberculosis.

He calls attention to some results of research which have been neglected. These concern the incidence of tuberculous infection among the general population, the difficulty of giving a prognosis, and the relatively poor results of present therapeutic measures, even in pulmonary tuberculosis in the early stages.

Under present circumstances, it is not feasible to isolate effectively all persons with static or intermittently open tuberculosis of the lungs. Moreover, persons infected with pulmonary tuberculosis may unexpectedly develop a rapidly progressive pulmonary process and so have time to infect a considerable number of persons before the diagnosis is established.

Without more effective economic aid to persons with tuberculosis and to susceptible groups of the population, and, without widespread BCG inoculation, photofluorographic examinations can hardly produce the desired results.

ZUSAMMENFASSUNG

Verf. betont als seine Ansicht, dass aus mehreren Gründen von einer die Gesamtbevölkerung umfassenden Schirmbilduntersuchung nicht so sehr viel zu erwarten ist. Er macht auf gewisse, offenbar allzu wenig beachtete Forschungsergebnisse über die Verbreitung der tuberkulösen Infektion in der Bevölkerung aufmerksam, sowie auf die Schwierigkeiten bei der Beurteilung der Prognose und die verhältnismässig geringe Wirksamkeit der heutigen therapeutischen Massnahmen selbst bei Lungentuberkulose in frühem Stadium.

Unter den heutigen Verhältnissen ist es nicht möglich, die ständig oder intermittent offenen Fälle in befriedigendem Masse zu isolieren. Es kommt noch hinzu, dass die Tuberkuloseinfizierten nicht selten ganz unerwartet einen rasch fortschreitenden Lungenprozess bekommen und viele ihrer Mitmenschen infizieren, ehe die Diagnose gestellt wird.

Ohne effektivere wirtschaftliche Unterstützung der Erkrankten und der besonders gefährdeten Bevölkerungsgruppen sowie umfassende BCG-Impfung sind von Schirmbilduntersuchungen kaum Ergebnisse von grösserem Wert zu erwarten.

RÉSUMÉ

L'auteur fait valoir que d'après lui, et pour plusieurs raisons, on n'est pas justifié à caresser de trop grands espoirs quant à l'utilité d'examens radiophotographiques englobant toute une population. Il rappelle quelques résultats, manifestement trop peu remarqués, des recherches portant sur l'étendue de l'infection tuberculeuse au sein de la population, sur la difficulté du pronostic, ainsi que sur l'efficacité, peut-être médiocre, de nos mesures thérapeutiques actuelles, même quand il s'agit d'un stade précoce de la tuberculose pulmonaire.

Dans les conditions actuelles il n'est pas possible d'isoler sur une assez grande échelle les cas de tuberculose pulmonaire ouverte, que celle-ci soit ouverte constamment ou par intermittence. Il s'y ajoute que les bacillaires voient assez souvent, et de façon tout à fait inattendue, leur poumon présenter un processus à marche rapide, de sorte qu'ils ont le temps de contaminer de nombreux humains avant que leur mal soit diagnostiqué.

Sans un secours économique plus effectif aux malades et aux groupes sociaux plus spécialement menacés, et en dehors d'une vaccination générale au BCG., on ne saurait guère attendre des examens radiophotographiques un résultat de valeur considérable.

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FROM THE RADIUM CENTRE FOR JUTLAND, AARHUS, AND THE MUNICIPAL HOSPITAL ROENTGEN DEPARTMENT, AARHUS, DENMARK (DIRECTOR: PROFESSOR CARL KREBS)

TOLERANCE DOSE PROBLEMS IN RADIOLOGICAL WORK[1]

by

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Personnel working with sources of ionizing radiation is exposed to certain occupational hazards because no protection can be rendered absolutely effective in practice. This applies particularly to work with radium and other radioactive substances, but also to some extent to exposure to roentgen radiation, as scattered irradiation cannot be completely eliminated. It has therefore been important to fix a permissible dose, which may be regarded as harmless or at least tolerable, and which may form the basis of the protective arrangements and the control of the efficiency and observance of such measures. This control is exercised partly by physical measurements of the amount of radiation and partly by health inspections, in which hematological examinations play a dominant rôle.

In the 1920's the so-called tolerance dose was determined empirically by MUTSCHELLER (1) and other investigators at approximately *0.25 r/day*. In 1937 this figure was maintained by The International Committee for Radiation Protection. However, during the last decade 0.1 r/day has generally been set as the maximum dose; this holds good, *e. g.*, of Great Britain, the U. S. A., and Scandinavia. In Germany two values are used, a »Toleranzdosis» = 0.25 r/day and an »Erbschädigungsdosis» = 0.025 r/day (2). Thus no absolute agreement exists as

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to the size of the dose, but there is a constant tendency to reduce it. In America a maximum dose of 0.02 r/day has been proposed, and in Sweden it has been suggested to fix a dose of 0.1 r/week by law (3).

The fixation of a certain limit of a small, harmless, but long-continued amount of radiation is still an open problem. The criteria for the harmful or harmless influence on the human organism of weak but daily irradiation are not yet known with certainty. During the last and present generations many people have been exposed to a slight irradiation through years without having suffered any apparent damage. Maybe the period of observation is too short. Several reports (4) of single cases of leukemia caused by radiological occupation and a report (5) from the U. S. A. of an increased incidence of leukemia in radiologists may in this connection give food for meditation. It must be endeavoured to reduce the unavoidable exposure to radiation to a minimum compatible with the execution of the work in practice and with the technical possibilities.

This is also one of the principal considerations in the argumentation for the reduction of the permissible dose in the Swedish proposal. Furthermore, the results of large series of blood examinations (6, 7) which constitute an important feature in the careful control of all radiological workers in Sweden, have also been a contributing factor in the desire for an alteration of the existing regulations. The Swedish authors (3) emphasize that it should not cause any difficulties to maintain a safety dose of 0.1 r/week. Exposure to a larger dose of irradiation of individual peripheral parts of the body may be permissible, if only the whole-body radiation is kept as low as about 0.1 r/week, *e. g.*, the hands may be exposed to about 1 r/day (8).

In the U. S. A. particularly the development of atomic energy has caused these problems to become of topical interest. A large number of workers are to be protected; through the protection and control of these workers new experience is gained, and moreover the problems are studied very carefully in large-scale animal experiments. These experimental studies have proved very valuable. In female mice exposed to 0.11 r/day (*i. e.* the »old» tolerance dose) over a prolonged period an increased incidence of ovarian cancer of about 70 % was found, as compared with the usual 8—10 % in the strain used. The tumours developed slowly and appeared in late life. In other experimental animals, chiefly guinea pigs, the sensitivity and reactions of the hematopoietic system to small daily radiation doses were studied. Doses of the order of 0.1 r/day did not produce definite changes, whereas exposure to 1 r/day induced distinct injury. According to the reports, mice and guinea pigs offer a great pathophysiological similarity to man in these respects. The examination of the personnel exposed to radiation showed

that no definite hematological changes were seen at dose rates below 0.1 r/day, but a further moderate increase in the dose was able to produce such signs of injury. The American authors (8, 9, 10) emphasize that the tolerance dose should not be set higher than 0.1 r/day and suggest that it should be reduced to 0.02 r/day, at least as far as females are concerned.

Protection and control measures are essential features in the activities of any radiological department. Therefore the discussion of the problems with regard to the size of the permissible dose has also induced us to consider the question. — In this hospital we have subjected the personnel to hematological examinations 4 times annually, and up to 1948 the individual exposure to radiation was measured 1—2 months every year. These measurements were carried out with pocket condensor chambers (11, 12). When planning this work continued measurements of the exposure to radiation parallel with the hematological examinations became desirable, and it was then decided to return to the method using small badges with roentgen films (1a, 14). These film badges have the advantage that they are not affected by a little moisture, which in a warm room may constitute a considerable and incontrollable source of error in ionizing chambers. The films may be worn for 1 or 2—3 weeks according to the amount of radiation to which the persons in question are exposed, while the condensor chambers are to be replaced every day.

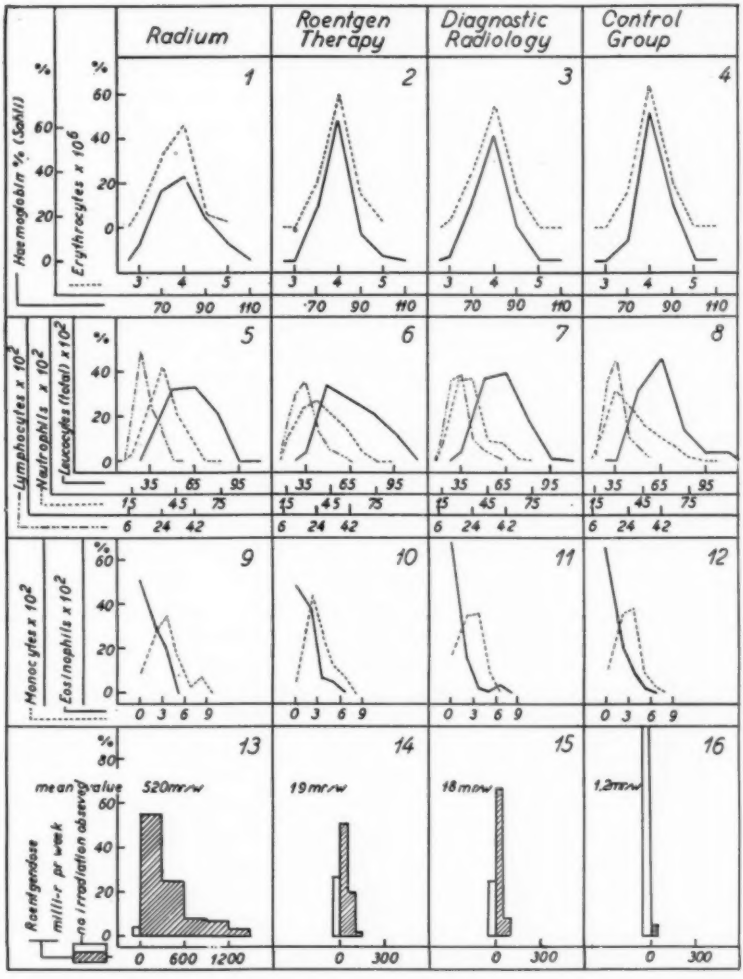
The blackening of the films varies according to the quality of radiation, while the ionizing chambers have the advantage to be comparatively independent of this factor. JACOBSEN & AMBROSEN (13) state that the condensor chambers show a variation in sensitivity of 7 % when the quality is changed between half-value layers of 0.12 and 1.4 mm Cu, which is also in agreement with our own experience. We have examined to which extent the blackening of the films depends on the quality of radiation by exposing a number of films to a constant amount of radiation but of different qualities. A dosage of 50 milli-roentgen (mr) and half-value layers of 0.05 mm Cu, 0.1 mm Cu, 0.7 mm Cu and 1.3 mm Cu results in a relative blackening of 1.2, 2.0, 1.6 and 1.2 respectively. If the qualities of radiation is assumed to be within the limits mentioned above, and the films are calibrated by a radiation with the half-value layer of 0.7 mm Cu, the dosage can be determined with an accuracy of $\pm$ 25 %. It must be expected that the personnel is exposed both to soft and hard qualities of radiation, and that means a narrowing of the margins of error. As the tolerance dose has been fixed by a rather rough estimate, it will in the first instance be sufficient to examine whether the exposures to radiation are essentially larger, in the vicinity of, or smaller than this tolerance dose. For this purpose the film method may offer a sufficient accuracy.

The measurements were carried out as follows: The films which have been worn by the personnel for 1—3 weeks are processed together with other films, which have been exposed to known doses of radiation of varying size. They are used for the calibration of the degree of blackening. By this procedure the error appearing when the measurement films and the calibration films are not processed under exactly the same conditions is avoided. The blackening of the films is measured in a Pulfrich photometer, in which the density of the two films can be compared. The exposed films are compared with an unexposed film, which has been processed together with the other films. The density of the exposed film, which can be read on the photometer, is thus a direct measure for the blackening of the photographic emulsion. For each series of measurements the density of the films exposed to known doses is plotted against the doses. By means of this curve the density of the films worn by the personnel gives the dosage.

Owing to the great difference in the sensitivity of the photographic emulsion to roentgen rays and gamma rays, the films worn by the personnel of the Radium Department must be treated separately. In this case the calibration films are exposed to radiation from 10 mg radium at a distance of 10 cm for varying periods of time. At the conversion to roentgen units the intensity of 1 mg radium at a distance of 1 cm is assumed to be equal to 8.4 r/hour.

The results of the measurements which extended over 15 months (March 1, 1949 to June 1, 1950) appear from the table, into which also the results of the hematological examinations have been entered. The four groups comprised the personnel from the Departments of Radium Therapy, Roentgen Therapy, and Diagnostic Radiology, and a control group consisting of non-exposed personnel (photographers and maids). The four groups consisted of 6, 10, 15, and 8 persons respectively. On these persons 37, 55, 75, and 44 hematological examinations were carried out at intervals of about 3 months. The total number of measurement weeks for which the personnel wore films which have been included in the calculations amounted to 308, 378, 636, and 219 respectively. A small number of films had to be discarded, generally because of unwanted illumination due to damage to the paper packing.

The protective measures taken in the various departments have been arranged along the usual lines. At the Radium Therapy Department all radium (= 1.2 g) is stored in a lead-protected lift car which is normally placed 5 metres underground. When radium is to be used, the car is hoisted up through a shaft on the outside of the building to the packing room on the first floor. When the desired quantity of radium has been taken from the car, this is again lowered to its place underground. All packing takes place behind a lead shield, 8 cm thick. — In the Roentgen



The results of hematological examinations and measurements of exposure to ionizing radiation are given in percentual distribution curves. In the hematological examinations the abscissas show the absolute number of the various blood cells per cu.mm. In the dosage measurements all zero values are shown as unshaded columns to the left of the zero point, the other values as shaded columns to the right of the zero point. The abscissas show milli-r per week.

Therapy Department there are 12 therapeutic units. The roentgen tubes are all enclosed in radiation-proof containers. The lower portion of the partition walls between the treatment rooms and the control rooms are covered with 4 mm lead, the upper portion with 2—3 mm lead. Tensions up to 180 kV are used. — In the Diagnostic Radiology Department we have 9 modern and 3 older units. The control desks are placed behind lead shields, 2—3 mm thick.

In addition to the measurements reported above we have also during the last 6 months measured the exposure to irradiation of the personnel of 4 wards where the patients stay during radium treatment. These measurements have not (as yet) been supplemented with systematic hematological examinations and are therefore not included in the table. In men's wards the average dose has been approximately 20 mr/week, in women's wards approximately 50 mr/week. The difference is due to the fact that more women than men are treated with radium (uterine cancer!).

All the examinations and measurements have been carried out in the hematological and physical laboratories of the Radium Centre, with a uniform technique and by the same persons throughout the whole period.

The evaluation of the results of the hematological examinations is rather difficult. In the course of time a large number of changes in the blood picture have been interpreted and described as consequences of a weak, but long-continued exposure to radiation. These changes have chiefly been numerical and morphological deviations from the normal, due to a more or less complete inhibition of the hematopoiesis or to abnormal maturation. Some authors make a distinction between irradiation damage proper and less pronounced, presumably irritative changes in the blood picture. It is unquestionable that changes may occasionally be encountered which must be regarded as irritative reactions, but it seems risky to reckon with two types of blood changes of different importance. It may be difficult to distinguish between them, and it may be justifiable to interpret an irritation as an expression of incipient or threatening injury. In addition, the normal variations in the blood picture are so wide that evidences of excessive irradiation, which are at first rather slight and slowly progressing, may easily be overlooked. It is therefore necessary to be on the look-out even for small deviations. This becomes even more important if the tolerance dose is reduced to 0.1 r/week, as the sensitivity of the hematopoietic system will then be considerably above the tolerance margin. — The hematological changes which must especially be emphasized as the first expressions of excessive exposure to ionizing radiation are:

1. *A persistent depression of the leukocyte count below 3—4,000.*
2. *A granulocytopenia in association with a low leukocyte count* (= *relative lymphocytosis*).
3. *An absolute lymphocytosis in association with an elevation of the leukocyte count above 12—15,000.*
4. *Anemia* (*Hemoglobin percentage below 65* %).
5. *An increase in the mean diameter of the erythrocytes* (= *a shift in the Price-Jones curve to the right*).
6. *Polycytemia* (*over 5,800,000 erythrocytes*).

(These statements are chiefly based on American and Swedish reports and are in accordance with our own limited experience.)

The combination and degree of these changes may vary from individual to individual and are, of course, of essential importance in the evaluation. If the exposure to irradiation is increased to daily doses of 0.5—1 r or more, severer reactions will be seen, increasing to partial or complete bone-marrow aplasia. Various morphological changes of the leukocytes, such as hypersegmentation of the granulocytes, vacuolation of the monocytes, »Dickie bodies» in the lymphocytes, etc., are often mentioned as evidences of excessive exposure. Such changes are not uncommon, but their diagnostic importance is rather uncertain. The said radiation injuries of the hematopoietic system are not expressions of any specific affection. Various »mitotic poisons», such as benzene, mustard gas (also nitrogen mustard) and several other compounds, may induce similar injuries.

The results of the hematological examinations of the personnel of our three radiological departments are shown in the above curves (Figs. 1—12). It will be seen that only the Radium group showed minor changes, in the form of a moderate tendency to anemia and indications of slight leukopenia. It will not be justifiable to draw other conclusions from the present small series. The two other groups do not present any abnormal variations. The curves for the control group correspond fairly well to what is usually considered normal (15, 16). It should be noticed that all the persons in the four groups were females.

The results of the measurements (Figs. 13—16) show that the Radium group was exposed to about 25 times as much radiation as the two other groups. The average irradiation was about 100 mr and 3—4 mr daily. If the tolerance dose is set at 100 mr/day, as has been done so far, the average exposure of the Radium group was at the upper limit of the tolerance range, but about 15 per cent of the measurements showed a considerable excess of the permissible dose, up to 2—300 mr per day. These high values originate almost exclusively from student nurses packing the radium preparations. For that reason the maximum period

for which they are engaged in radiological work is set at three months in order to safeguard them against radiation damage. Apart from the student nurses, the average exposure of permanently employed nurses was about 70 mr/day. If the permissible dose is to be reduced to 100 mr/week (= 20 mr/day), it is obvious that the protective measures and working methods in the Radium Therapy Department are to be revised. (Recent examinations have shown that the transport of the radium preparations from the packing room to the operating room and the mode of storage in the operating room are the weak points.) In the two other departments alterations in the working conditions need not be considered as the average dosage of 20 mr/week is well below the reduced tolerance dose.

Thus the results of the hematological examinations and of the measurements of radiation show good agreement. In the two groups which have only been exposed to slight irradiation the blood picture shows no evidence of excessive exposure, but corresponds to that of the non-exposed personnel. In the Radium Therapy group moderate hematological changes due to irradiation were found in a small number of the examinations, corresponding to the fact that some of the persons in this group have been exposed to considerable amounts of irradiation. A close study of the individual results did not reveal any serious radiation injury. All the changes encountered were reversible and subsided after iron therapy, etc., and additional vacations. The maintenance of the running transfer of the student nurses to other non-radiological departments is very important. Really severe and continued excesses of the tolerance range, which nowadays simply means carelessness in some way or other (17, 18) have not been observed.

On the whole, it may be said that a reduction of the permissible dose seems well-founded. The sensitivity of the hematopoietic system to irradiation must certainly be supposed to be above the dose so far permitted = 100 mr/day, but all the same alarmingly close to it. The »Mutscheller» tolerance dose = 200—250 mr/day is obviously too high. The possibility of induction or acceleration of ovarian tumours and leukemia is a serious argument in the discussion. The accomplishment of the reduction need not be attended with insurmontable difficulties, especially not as far as roentgen departments are concerned, while it may cost some more trouble with regard to work with radium and other radioactive substances.

As exposures to doses of the order of 100 mr/week will not induce any demonstrable hematological changes, it must be considered expedient to check the exposure of the personnel by continued physical measurements, which must also be supposed to be of some educative value. The use of film badges seems to give a sufficient accuracy and

constitutes a convenient and time-saving method. However, the hematological examinations cannot be dispended with; they will still be the most important available biological control measure, although their diagnostic value with a view to the control of smaller excesses of the tolerance dose will be reduced.

SUMMARY

A series of hematological examinations and measurements of the exposure to ionizing radiation of the personnel of the Departments of Radium Therapy, Roentgen Therapy, and Diagnostic Roentgenology, Aarhus, is reported. It is shown that the tolerance dose, which has so far been set at 100 mr/day, is fairly close to the limit of the sensitivity of the hematopoietic system.

Since, as reported by other investigators, a risk of other harmful effects of exposure to radiation of this order of magnitude must be taken into consideration, it is proposed to reduce the tolerance dose to 100 mr/week.

ZUSAMMENFASSUNG

Es wird über serienmässige Blutuntersuchungen und Messungen der Ionisations-Strahlung berichtet, denen das Personal an der Abteilung für Radium-Röntgen-Therapie und für Röntgen-Diagnostik, Aarhus, ausgesetzt war. Es hat sich erwiesen, dass die Toleranz-Dosis die bisher mit 100 mr/täglich festgesetzt war, an der Grenze der Empfindlichkeit des haematopoetischen Systems liegt.

Da, wie von anderen Forschern berichtet wird, auch an die Gefahr weiterer Schädigungen als Wirkung einer Strahlung in dieser Grössenordnung gedacht werden muss, wird die Verkleinerung der Toleranzdosis auf 100 mr/wöchentlich vorgeschlagen.

RÉSUMÉ

Relation d'une série d'examens hématologiques et de mesures du degré d'exposition au radiations ionisantes, portant sur le personnel des Divisions de Radiumthérapie, de Radiothérapie et de Radiodiagnostic, Aarhus. Il en résulte que la dose tolérable, fixée jusqu'ici à 100 mr. par jour, approche beaucoup de la limite de sensibilité du système hématopoiétique.

Étant donné que, selon d'autres communications, il faut tenir compte du risque d'autres effets nocifs encore lorsque l'exposition aux radiations est de cet ordre de grandeur, la proposition est faite de réduire à 100 mr. par semaine la dose tolérable.

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FROM THE CENTRAL INSTITUTE OF RADIOTHERAPY, HELSINKI, FINLAND
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A CASE OF MELORHEOSTOSIS[1]

by

Marja Koulumies

In 1922 LÉRI and JOANNY described a disease of the bones which they called melorheostosis. Recognition of the disease is possible only by roentgen examination. In typical cases an osteosclerotic, structureless dense stripe, like flowing candle-grease, is seen along the bones of the limb parallel with its longitudinal axis, usually along a specific side of the bones. The outline of the affected bone is altered. Frequently one limb only is involved (KÖHLER, FAIRBANK). Mild or more or less severe pain is usually present in the affected part and the movement in the adjacent joints is restricted.

The pain usually appears in young persons, sometimes already in childhood. The age of the patients in recognized cases was reported by KÖHLER to have been between 8 and 56 years and by FAIRBANK between 5 and 54. The latter specifically pointed out that three-fourths of the 47 known cases occurred before the age of 36. The disease probably begins in all cases in childhood; and in at least some cases it has been found to have started already at the foetal stage. In three cases a deformity was present at birth in a finger of the hand in which typical melorheostosis was diagnosed later (FAIRBANK). The disease is progressive. It is not limited to sex but it is more common in males than in females (FAIRBANK, NATVIG). No relation has been found to heredity.

The etiology of the disease is not known but a number of theories have been presented. Ischemia secondary to local disturbance of the sympathetic system was suggested by PUTTI, whereas LÉRI stressed that in his cases no changes were present in the nervous system and that the area of increased density had no relation to the course of a nerve or a blood vessel ramification. MOORE and LORIMIER believed it to be due to local subperiosteal telangiectases. FEJÉR in his case suspected con-

[1] Submitted for publication, June 28, 1950.

nection with an earlier cranial trauma, which through the intermediary of the cerebral caudex and the parathyroids probably gave rise to the pathological condition. ZIMMER's theory that melorheostosis develops on the basis of a disturbance in the embryonal metameric development has obtained the widest acceptance.

The disease is extremely rare. According to FEJÉR (1948) 26 cases have been published but FAIRBANK (1948) knows of 47 cases, at least one of which he nevertheless regards as doubtful. In October 1948 a typical case of melorheostosis — the first one known in Finland — was diagnosed at the Central Institute of Radiotherapy in Helsinki and its publication here may be of interest.

Case Report. The patient, the wife of an agricultural technician, was 35 years of age. The anamnesis revealed no hereditary features of interest. The patient had generally been in good health and had three healthy children. She had suffered no cranial traumas. The menses were regular. According to her parents *the thumb of her right hand had been crushed in a door when she was a few years old, since which the terminal phalanx and the nail had been deformed.*

Ten or more years ago the patient began to notice the formation of a protuberance in her right elbow, associated with slight pain. She consulted a doctor and the roentgenogram then taken (1938, patient 23 years of age) shows compact tuberous osteal hypertrophy in the radius of the right forearm, in the multanguli, and in the metacarpal of the thumb, which is partly visible in the roentgenogram. No other bones were photographed nor was the disease diagnosed as melorheostosis. Roentgen therapy was applied to the right forearm and upper arm because of the pain. She was in good health until the summer 1947, when the pain in the right forearm and upper arm recurred and renewed growth was noted in the old osteal protuberances. Irradiation was resumed but the pain did not subside. In October 1948 the patient consulted the Central Institute of Radiotherapy in Helsinki.

Status praesens: The patient's general condition was good. She was 159 cm tall and weighed 53 kg. There were no palpable lymph glands. The blood pressure was 120/90 mm Hg. No goitre was present. No neurological features of interest were observed. The laboratory tests gave the following analyses: SR 8/24; Hgb. (Sahli) 68; Erythroc. 4.11 mill. Colour index 0.81; Leucoc. 3,200. Diff.: Neutroph. 63 per cent (Segment 60 per cent, Stab. 3 per cent, Juv. —), Eosinoph. 4 per cent, Basoph. —, Monoc. 7 per cent, Lymphoc. 26 per cent; Blood Ca 9.9 mg and blood P 3.8 mg per 100 cc.; Basal metabolic rate + 13 per cent; WR —, Kahn —.

A hard, tuberous dense area could be felt along the length of the radius of the right arm and the bone was somewhat curved. *The tip of the right thumb was deformed and thick and the nail also was deformed.* The patient complained of occasional mild pain in the right forearm and the right thumb, particularly when fatigued by rotary motion. At examination the humeral articulation was free but movement in the cubital articulation, especially pronation and supination, was partly restricted. The same was true of abduction of the thumb. The movements were not painful and the bones were not tender to pressure.

The roentgenograms (Figs. 1 and 2) showed osteosclerotic, structureless, dense bone along the radial side of the right humerus, radius, radial carpals, first metacarpal, and phalanges of the pollex. In the long bones it had the typical form of flowing candlegrease. No changes were present in the bones of the right shoulder, the upper left limb,

Fig. 1.

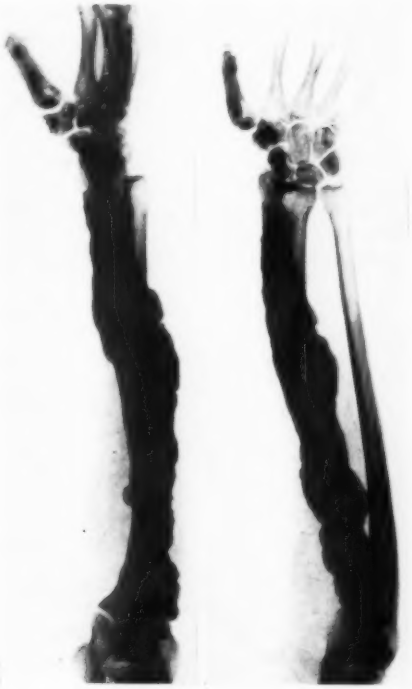

Fig. 2.

or the thorax, pelvis or lower limbs. Comparison of the roentgenograms taken of the right antebrachium in 1938 and 1948 revealed increased tuberosity in the contour of the radial protuberance, indicating slight progressiveness of the disease.

A biopsy made of the protuberance in the radius showed the bone to be quite hard. P. A. D.: The specimen contained loose pieces of bone, which were compact in density. Similar bone was found in the muscle interstice at one point (I. WALLGREN).

The disease here described is a typical case of melorheostosis of the upper right limb. No cranial trauma was present but a notable feature was the severe trauma of the thumb of the right hand received in childhood and the deformity present in the terminal phalanx and the nail of this thumb. FAIRBANK reported digital deformity in 7 of the 16 cases of melorheostosis of the upper limb and KÖHLER published a case in which he suspected a local trauma of being the cause of this disease in one of the upper limbs. A similar probability offers itself in the present connection, although it should be held in mind that the trauma in the

patient's thumb had taken place in early childhood and there is of course a possibility that a slight deformity was present in the thumb already earlier, perhaps congenitally, but was not noticed until in connection with the trauma.

SUMMARY

Report of a case of melorheostosis of the upper right limb, characterized by a severe trauma of the thumb of the right hand in childhood. Examination revealed deformity of this digit and melorheostosis along the radial side of the bones of the upper right limb. This suggests a relation between the trauma and the development of the disease, as the changes in the bones were on the corresponding side.

ZUSAMMENFASSUNG

Es wird ein Fall von Melorheostosis der rechten oberen Extremität beschrieben, bei welchem in der Kindheit ein schweres Trauma des rechten Daumens vorgekommen war. In dem Daumen wird Missbildung und proximal davon in den Knochen auf der Daumenseite der rechten oberen Extremität Melorheostosis festgestellt. Dieser Umstand erweckt den Verdacht, dass das Trauma mit der Melorheostosis in ätiologischem Zusammenhang stehe, weil sich die Veränderungen gerade auf der entsprechenden Seite befinden.

RÉSUMÉ

Description d'un cas de mélorhéostéose de l'extremité droite superieure dont le trait distinctif est un grave trauma du pouce droit pendant l'enfance. A l'examen on a pu constater une déformation de ce doigt et de la mélorhéostéose dans les os de l'extremité droite superieure, du côté du pouce. Ceci fait supposer un rapport entre le trauma et le developpement de la mélorhéostéose, étant donné que les altérations se trouvent juste du côté correspondant.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR: BENGT HOLMGREN) AND THE CLINIC LABORATORY (DIRECTOR: BO NORBERG) OF SABBATSTERG HOSPITAL, STOCKHOLM, SWEDEN

AN ATTEMPT OF EXCRETING INJECTED THOROTRAST IN RABBITS BY 2, 3-DIMERCAPTO-PROPANOL (BAL)[1]

by

Björn E. W. Nordenström-Blomqvist

The introduction of different injectable radioopaque drugs has been of great importance in roentgen diagnosis. Many problems in connection with this are still far from being solved. In connection with the development of modern roentgen diagnosis of the heart and vessels, radiologists and chemists have been compelled to try new ways. Against this background it is to be understood with what enthusiasm one saw the development of the injectable thorium compounds, of which the first was described in 1929 by BLÜHBAUM, FRIK and KALKBRUNNER (2). One of the best thorium compounds was manufactured by Heyden under the name of Thorotrast (15). With its great opacity for roentgen and chemical indifference (7) it promised to become the best compound for visualization of the vessels.

Besides its chemical indifference and great opacity for roentgen rays, thorotrast is an excellent compound for visualization of the spleen and liver. The expectations of further clinical use of thorotrast have failed. The thorium dioxide is fixed mainly by the reticuloendothelial cells, and this for a long time. In connection with its physical property of radioactivity one has experimentally produced serious damages of the cells of the reticuloendothelial system. Sarcoma and cirrhosis are provoked in animals (23). Acute symptoms after injection of thorotrast as slight fever, anaphylactic symptoms and purpura are seen. Following this, many authors have abandoned the use of thorotrast as a diagnostic aid. It is therefore practically unused in human practice. One case of mammography is described, where later, on account of suspicious malignancy, one had to perform an amputation of the mamma. REEVES and STUCK

[1] Submitted for publication, July 24, 1950.

(18) have in 1938 written a monograph on the thorotrast literature ten years after the introduction of thorotrast as a roentgen diagnostic aid. Their opinion of the clinical use of thorotrast was lacked enthusiasm. JONSELL and LINDGREN (10) have described a case of lienohepatography which came to section 10 years after the injection of 75 ml of thorotrast. Cirrhosis of the liver and degenerative changes in the portal glands and the spleen were found. The patient, an 84-year-old woman, had had clinical signs of thorium damage and died of senility and bronchopneumonia. MAC MAHON, MURPHY and BATES (12) have in 1947 described a case of primary malignant endothelial cell sarcoma of the liver in a 68-year-old woman, who ten years earlier had had a gumma in the liver visualized after thorotrast injection. To this report, however, Dr H. Y. GOLDSTEIN has added: »The many gallons of spirocheticidal remedies administered might also cause some liver changes.» In spite of the spreading use of thorotrast during the first ten years after its introduction, there is still not one really proved case of primary malignant tumor in man caused by thorotrast.

The experimental results in animals, where one has succeeded in getting malignant degeneration, should however not be forgotten, and a reintroduction of thorotrast in human practice is not for the present. There is still a latent risk of degeneration in those, who have received large doses of thorotrast during the thorotrast era in the early part of 1930.

Experiments are being performed in order to remove the thorium dioxide chemically under acidosis. The effect was insignificant. Parathyroid hormone has also been used to remove the thorium dioxide from the storage place in the bones, but with negative results.

The progress of the chemical research during the second world war has also made a contribution to the treatment of different kinds of metal poisoning.

EHRLICH developed in 1909 the theory that the toxic effect of arsenic was due to its affinity for certain sulfhydryle groups of importance in tissue oxidation. PETERS and al. (16) have found that dithiols have a greater affinity for arsenic than monothiols. By the binding of arsenic and dithiols there is also a marked desintoxication of arsenic. They proposed the theory that arsenic could be removed by binding it to a synthetic dithiol in case of arsenic poisoning. With this background 2,3-dimercaptopropanol or British Anti-Lewisite (BAL) was synthesized. This substance has the ability of increasing the excretion of arsenic and desintoxicating, in cases of arsenic poisoning (13, 16, 19, 24). This quality of BAL has later on shown to be applicable to several kinds of poisoning with special heavy metals, such as gold (6), mercury (3, 8), lead (1, 21), chrome, nickel, antimony and bismuth (3). BAL has been in effective in thallium and selenium poisoning.

Certain circumstances speak of the possibility of using BAL also in thorium poisoning. Thorium stands in a certain relation to lead, which can be removed by BAL. This is the case in cronic lead poisoning (1, 21). Also other circumstances as the similarity of the storage of thorium and lead in the organs are established. These facts have led to an experiment consisting of removing intravenously injected thorotrast in rabbits with BAL.

Method

In these experiments rabbits of about the same weight were used. Each was placed in a cage and fed with hay and turnips. The amount of turnips was adjusted such as to obtain about 100 ml of urine per day. The animals received 1 ml thorotrast per kg body weight intravenously. The urine was collected every day and its radioactivity determined.

Thorotrast (Heyden) consists of 25 % thorium dioxide in a stable emulsion. The thorium dioxide is adherent to colloidal particles of several polysaccharides, with physical qualities similar to those of blood.

LEIPERT has measured the alpha-activity in 25 ml of thorotrast equivalent to 0.5—1 micrograms of radium. TAFT (22) has determined the gamma-activity in 75 ml thorotrast equivalent to 1.37 micrograms of radium. Thorium however is disintegrating to new radioactive elements in the thorium series and the lowest alpha-activity is found in 4—5 years old thorium (18).

2,3-dimercaptopropanol from Boots Pure Drug Comp. was used. It consists of 5 % solution in arachis oil containing 10 % benzyl benzoate to acid solution. It was administered intramuscularly. The total amount of BAL varied between 10—100 mg per day and was given in three equal doses with 3—4 hours' interval.

The determination of the radioactivity was performed with an instrument set made by Technical Associates, 3,730 San Fernando Road, Glendale 4, Calif. Geiger Counter Scaling unit, Model G. S. 4. with lead-shield Model L S—1 and ratemeter Model R M—3 were used. The Geiger tube used was from the same manufacture, Type T A B 1 with a background of usually 20 impulses per minute.

The radioactivity was determined on round metal plates of 27 mms' diameter and a center distance to the window of the tube of 10 mm. The determinations were made during at least 10 minutes.

The urine from the animals was collected in porcelain-crucibles. After evaporating to dryness, the crucibles were placed in an oven at about 600° C. for 24 hours. The amount of ash per day and animal was usually 1—3 gm. After mortaring the ash carefully, 0.5 gm of it was placed on the metal plate and spread to a thin layer covering the whole bottom of

it. The activity in the sample was then determined and the corresponding value for the whole amount of ash calculated.

The Excretion of Radioactive Elements in Urine after Injection of Thorotrast

The correlation between the counts and different amounts of thorotrast is shown in diagram 1 A. The thorotrast is pipetted on the metal plate and evaporated to dryness at room temperature. In order to avoid unequal distribution by adherence to the walls of the plate a thin line was drawn with a waxpencil on the inside of the plate in the angle between the bottom and the wall. A uniform layer of thorotrast could thereby be obtained. The counts showed a direct proportionality to the amount of thorotrast.

The homogeneity of the radioactive material in the ash is shown in diagram 1 B. As many 0.5 g portions as possible were taken from the same urine preparation and counted. An acceptable uniformity in the dispersion of the radioactive material was found.

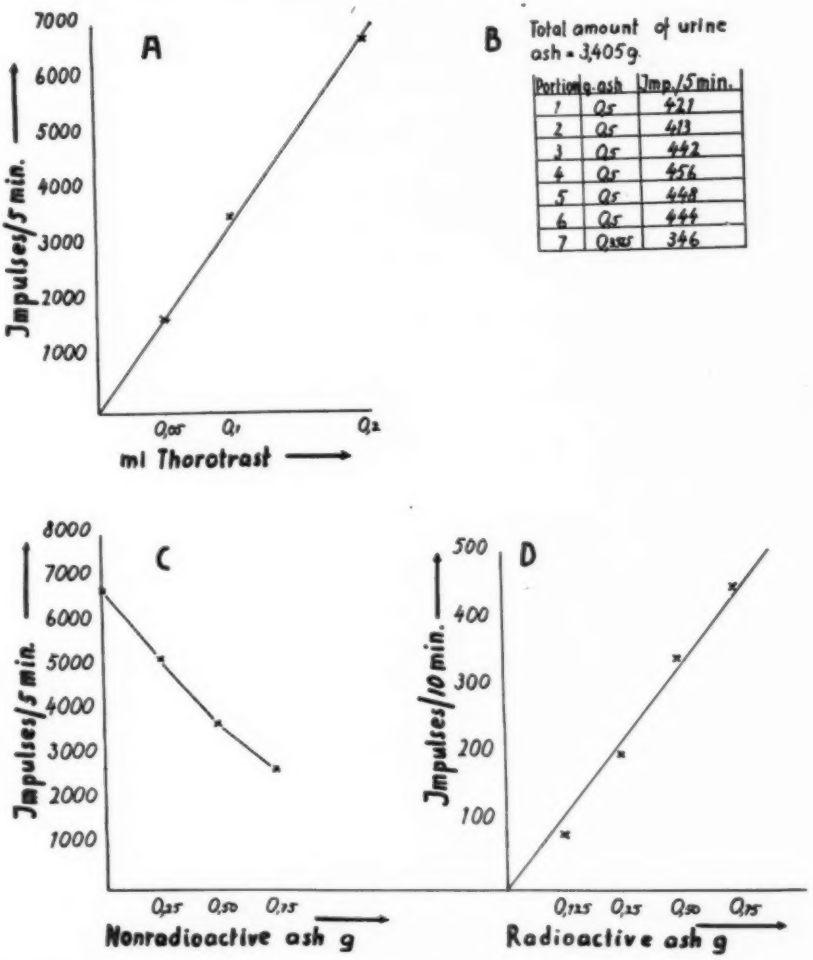
According to the high alpha-intensity of thorium, a considerable checking by the ash is to be expected. To determine the maximum checking effect of the ash, 0.2 ml of thorotrast was evaporated on a plate as previously described. It was then covered with different layers of non-radioactive urine ash. Diagram 1 C shows the checking effect of the ash. 0.5 g of ash causes a decrease of the activity of about 50 %.

When 0.05 ml of evaporated thorotrast were mixed with 0.5 g of non-radioactive urine ash, the decrease of the radioactivity was 32 %. The same sample of thorotrast mixed with 1.5 g of non-radioactive ash showed a decrease of 51 %. Thus the checking effect of urine ash upon the radioactivity of thorotrast is considerable.

The radioactive measurements were performed 36 hours after the collection of the urine. It could be expected that in case of excretion of thorium in the urine the high checking of the alpha rays by the ash should make the quantitative determination hazardous. Surprisingly that was not the fact in ash three weeks of age. (Diagram 1 D.) There was instead a direct proportionality between the counts and the amounts of ash. A small discrepancy from the proportionality was however found in ash 36 hours of age, but the values could be accepted as sufficient for the investigation intended.

STENSTROM and VIGNESS (20) have examined the elimination of radioactive elements in patients who had received thorotrast intravenously. No excretion of thorium could be shown. Disintegration products of thorium were however found. Thorium X was identified as the dominating element in faeces, and thorium B was found in the expired air.

Diagram 1



A. There is a direct proportionality between the amount of thorotrast and the count.
B. Different portions from 3.405 g radioactive ash. The ash is homogeneous in regard to its content of radioactive material.
C. The maximum checking effect of urine ash. 0.2 ml of evaporated thorotrast is covered with different amounts of non-radioactive ash. The counts are decreasing proportionally to the thickness of the ash layer.
D. Different amounts of radioactive ash show a direct proportionality to the count in 3 weeks old urine ash.

A sample of ashed urine showed radioactivity but was not further examined.

With respect to the shown direct proportionality between the counts and the amount of urine ash three weeks of age, there is probably no alpha radiation of importance in this ash. For the same reason thorium can be excluded as the direct source of the radioactivity in the ash. It is probable that the radioactivity in the urine is due to some disintegration product of thorium.

For further analysis of the radiation of the ash, it was filtered with 2 mm of lead (table 1). The leadfilter showed a little radioactivity itself. After filtering the radioactive ash, there was a complete checking of the radiation. Any gamma radiation could therefore not be shown. With the same leadfilter there was shown a gamma-intensity in the used thorotrast amounting to 7.3 % of the total radiation. The intensity of the total radiation was low in the ash, but after filtering, there should be a measurable activity calculated on the relative gamma-intensity of the injected thorotrast.

Radioautographs of the ash were also made. The time of exposure varied from one day to several weeks. Microscopic examination showed beta traces on the film, but any traces of alpha particles were not seen.

Table 1

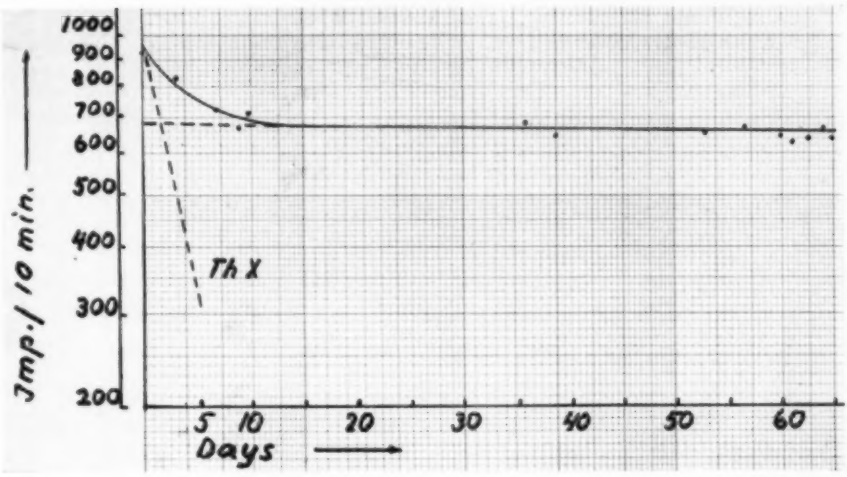
Urine Nr.	Background per min.	Impulses per min.	Background per min. (2 mm Pb).	Impulses per min. (2 mm Pb).
1	20.3	88.5	22.0	21.6
34	18.0	79.0	24.1	25.0
35*	22.0	58.4	24.1	25.0
36	22.0	75.8	24.0	24.2
37*	18.1	73.0	24.1	24.7
38	19.0	67.8	24.2	21.9
39*	17.9	59.6	23.3	22.4
40	18.5	77.4	24.2	22.3
41*	20.0	78.0	23.6	25.4
Thorotrast 0.1 ml.	22.6	409.9	22.0	51.9

* = urine from animals during BAL treatment.

In order to get a better idea of the course of the excreted radioactive element, a sample of urine ash was followed up for two months.

The curve in diagram 3 is decreasing rather rapidly in the beginning. After about two weeks it shows an almost constant value. The first rapidly decreasing part of the curve corresponds very well to some short-lived element in the thorium series. The only element in question is the

Diagram 3



same element previously found in faeces by STENSTROM and VIGNESS, thorium X, with a half life of 3.63 days. (Table 2.)

Table 2

Thorium disintegration series

Thorium	232.12	90	Alpha	1.65×10^{10}	years
Mesothorium 1	(228)	88	Beta	6.7	years
Mesothorium 2	(228)	89	Beta-gamma	6.13	hours
Radiothorium	(228)	90	Alpha-beta	1.9	years
Thorium X	(224)	88	Alpha	3.64	days
Thoron	(220)	86	Alpha	54.5	seconds
Thorium A	(216)	84	Alpha	0.145	seconds
Thorium B	(212)	82	Beta-gamma	10.6	hours
Thorium C	(212)	83	Alpha-beta	60.5	minutes
Thorium C'	(212)	84	Alpha	10^{-11}	seconds
Thorium C''	(208)	81	Beta-gamma	3.20	minutes
Thorium B (thorium lead)	(207.77)	82	Stable		

Compiled from FAJANS 1922, and RUTHERFORD 1930.

The flat part of the curve can only be caused by some longlived element, *e. g.* mesothorium I (half-life 6.7 years) and radiothorium (half-life 1.9 years). Mesothorium I emits only beta rays, while radiothorium emits alpha and beta rays.

Alpha radiation, which was not found in three weeks old ash speaks in favour of mesothorium I as the predominant longlived radioactive element excreted.

After intravenous injection of thorium (thorotrast) there is yet no excretion of thorium demonstrated. The radioactive element in the expired air and the faeces have been disintegration products of thorium. Analogous conditions seem to exist concerning the excretion of radioactive elements of the thorium series in urine.

The Excretion of the Longlived Radioactive Element in Urine from Rabbits during BAL Treatment after Injection of Thorotrast

Two rabbits of the same litter were used for the experiment. They weighed respectively 3,190 g (I) and 3,500 g (II). Both of them received 3 ml of thorotrast *i. e.* about 1 ml per kg bodyweight. This corresponds to a big clinical dose used in man, viz. 75 ml given to an adult (17).

The radioactive determinations were made 36 hours after the urine had been collected to avoid too great disturbance by shortlived disintegration products of thorium.

Diagram 4 A shows a radiogram taken of one of the used animals before injection of thorotrast. In the next picture, 4B, the liver and

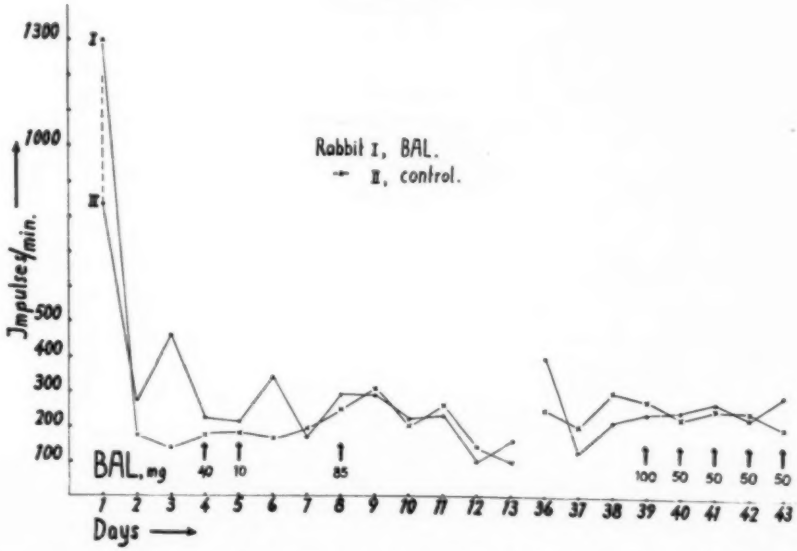
Diagram 4

A B C

spleen of the same animal are visualized one day after the injection of thorotrast. Diagram 4C shows the same animal 4 days after the injection. It is to be noted that the spleen has moved considerably in the abdomen.

The results of the experiment appears from diagram 5.

Diagram 5



The radioactivity in the urine per day after injection of 3 ml of thorotrast in two rabbits. Rabbit No. I was BAL treated.

The radioactivity in the urine during the first day is 3—4 times higher than during the following days. The first value for animal II is probably only $^2/_3$ of the real value, when about $^1/_3$ of the urine was lost before the evaporation. The activity is relatively constant $1^1/_2$ months after the injection of thorotrast. Animal II, which was a little heavier than No. I showed on the average a higher excretion per day.

In animal I after injection of totally 35 mg of BAL, divided in 3 doses per day on the 5th, 6th and 8th day there was no certain change in the curve of excretion. The experiment was therefore interrupted for three weeks but the radioactivity in the urine was as late as one month after the injection of thorotrast on the average of the same value as on the second day.

Then the doses of BAL were increased considerably. During five days 300 mg of BAL were administered. A total dose of 435 mg of BAL was

then given to the animal. This amount of BAL corresponds to about five times the dose given in human practice, for instance in cases of mercury poisoning. No changes of the radioactivity in the urine were seen. As previously shown in table 1 the radiation of the urine ash is totally screened by 2 mms of lead as well in the ash from the BAL treated animal as in that of the control animal.

The Radioactivity in Some Organs in Rabbits after Injection of Thorotrast and BAL Treatment

Radioactive elements are excreted not only in urine after injection of thorotrast. They also appear in faeces and expired air.

As a control, to make sure that the thorotrast was not excreted in unknown ways from the BAL treated animal, determinations were also made of the residual radioactivity in some organs.

Experiment No. 1 was terminated by killing the animals by intravenous injection of air. Some organs were taken out and ashed as a control of the remaining content of thorotrast. The result of the experiment is shown in table 3.

Table 3

Organ	Fresh weight, gm	Impulses per min.	Impulses per min. (2 mm Pb)	Gamma-intensity per gm
Yellow bone marrow ...	0.49	43.4	(4.0)	
Yellow bone marrow (BAL treated)	0.63	62.2	(0.0)	
Spleen	1.67	313.0	6.8	4.07
Spleen (BAL treated)...	1.72	404.1	6.3	3.65
Kidney	9.07	12.2	(1.0)	
Kidney (BAL treated) ..	10.26	10.8	(0.4)	
Liver	98.79	4575	108.0	1.09
Liver (BAL treated)....	120.05	4367	111.6	0.93

Any certain demonstrable difference of the radioactivity of the organs of the BAL treated animal and the control animal was not found. The radioactivity per g of fresh organ is four times as high in the spleen as in the liver. Chemical analysis of the thorium content in different organs of rabbits injected with thorotrast were performed by LEIPERT (11). He found nine times as much thorium in the spleen as in the liver. Using an electroscope the same author was not able to find any radioactivity in the urine after intravenous thorotrast injection.

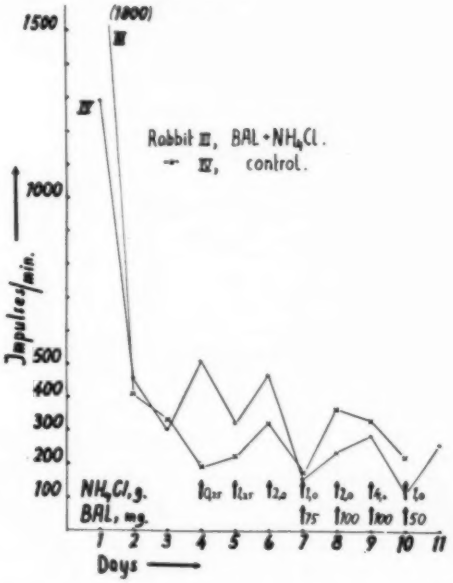
The kidney had a remarkable low radioactivity in both animals.

An Attempt of Removing Injected Thorotrast in Rabbits by BAL during Administration of NH_4Cl

American authors have maintained that increased excretion of lead was not found in cases of lead poisoning during BAL treatment. SUNDIN (16) reports that in cases of lead poisoning, he could considerably increase the lead excretion by BAL treatment during acidosis.

According to that, an experiment was made to remove injected thorotrast. The carbon dioxide combining power of the blood plasma was not followed up during the experiment. The doses of NH_4Cl administered were however considerable. On the average there was given more than ten times as much per kg bodyweight and day as is usually sufficient for producing acidosis. The animals were of about equal size. (Animal III, 3,637 g. Animal IV, 3,143 g.) The injected dose of thorotrast was the same as previously, 3 ml.

Diagram 6



The radioactivity in the urine per day after injection of 3 ml of thorotrast in two rabbits.
Rabbit No. II was BAL treated during administration of NH_4Cl.

The result of the experiment is seen in diagram 6. The doses of BAL and NH_4Cl represent the total doses per day.

No signs of increased radioactivity in the urine of the animal injected with thorotrast was found after BAL and NH_4Cl treatment. The excretion curves were of the same type as in the previous experiment.

Results

1. No excretion of thorium in urine is found.
2. The radioactivity in the urine consists of disintegration products of thorium of which one shortlived element, probably thorium X, and one longlived element, probably mesothorium I are excreted.
3. After an intravenous injection of thorotrast in rabbits, there is no increased radioactivity in the urine after BAL treatment, or after BAL treatment during administration of NH_4Cl.
4. The excretion curves of the radioactivity in the urine show the first day after injection of 1 ml of thorotrast per kg bodyweight a value 3—4 times as high as during the following days. The value is then relatively constant as late as one and a half months after the injection.
5. There was no significant difference between the remaining radioactivity in the liver, the spleen, the kidney and the yellow bonemarrow of one BAL treated animal and the same organs of the control animal.
6. The spleen shows a radioactivity four times as high as the liver, measured on the gamma-intensity per g. The kidney shows an apparent low radioactivity per g fresh weight in comparison with that of the liver and spleen.

SUMMARY

An experimental attempt was performed to excrete intravenously injected thorotrast in rabbits by 2,3-dimercaptopropanol (BAL). No excretion of thorium was found in urine. The radioactivity in urine depends upon disintegration products of thorium, of which thorium X and mesothorium I were found. After BAL treatment there was no sign of increased radioactivity in urine or significant decrease of the radioactivity in liver, spleen, kidney or yellow bone marrow. The radioactivity of the spleen was four times as high as that of the liver, measured on the gamma-intensity per g. The radioactivity of the kidney was low in comparison with that of the liver and spleen.

ZUSAMMENFASSUNG

Ein am Kaninchen ausgeführtes Experiment hatte zum Zweck das intravenös injizierte Thorotrast mittels 2,3-dimercaptopropanol (BAL) zur Ausscheidung zu bringen. Im Urin hat man keine Thoriumausscheidung nachweisen können. Die Radioaktivität im Urin wird durch die Thoriumzerfallsprodukte verursacht. Ein Element von kurzer Lebensdauer (Thorium X) und ein Element von langer Lebensdauer (Mesothorium I) werden ausgeschieden. Eine gesteigerte Radioaktivität im Urin nach BAL-behandlung konnte man nicht nachweisen. Die Radioaktivität der Leber, Milz, Niere und des gelben Knochenmarkes wurde nach BAL-behandlung nicht beeinflusst. Die Radioaktivität der Milz ist 4 mal grösser als die der Leber, berechnet per Gammaintensität und Gramm. Die Radioaktivität der Nieren ist sichtbar niedriger als die der anderen untersuchten Organe.

RÉSUMÉ

Ce travail porte sur un essai expérimental de provoquer l'excrétion du thorotrast injecté par l'intermédiaire du 2,3-dimercaptopropanol (BAL). Aucune trace de thorium n'a été retrouvée dans les urines des animaux en expérience. La radioactivité des urines provient de la desintégration du thorium dans l'organisme en un élément de vie très courte, le thorium X, et un élément de vie plus longue, le mésothorium I. On n'a pas pu constater d'augmentation de la radioactivité dans l'urine des lapins après le traitement par le BAL, ni de différence significative entre la radioactivité du foie, de la rate, des reins et de la moelle osseuse dans un lapin traité par le BAL et le lapin de contrôle. La radioactivité de la rate s'est révélée quatre fois plus grande que celle du foie. La radioactivité des reins était nettement inférieure à celle du foie et de la rate.

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FROM THE RADIOLOGICAL CLINIC (DIRECTOR: DR. OLOF SANDSTRÖM) OF THE CENTRAL HOSPITAL, ESKILSTUNA, SWEDEN

A UNIVERSAL DIAPHRAGM FOR DEEP ROENTGEN THERAPY[1]

by

Olof Sandström

In the Acta Radiologica the author has 1939 reported the construction of a diaphragm for deep roentgen therapy (1). The demands to a diaphragm for universal use in therapy, which have led to the construction mentioned above, are to a still greater degree valid even to-day. The modern fractionated treatment with multiple fields demands a careful adjustment of the beams and their screening-off to obtain a dosage as exact at the focal lesion as possible.

For this purpose a both surveyable and easy procedure is necessary. This is enabled by lighting of the field to be treated, the lighted field exactly corresponding to that of the roentgen-ray beam. Through the lighting of the field the treatment is easy to control.

The diaphragm construction has also come from the necessity of an easily manageable instrument which can replace the good old manual lead-rubber cover but at the same time keep up as far as possible its prominent qualities (variation of field and an exact protection of the surrounding tissue). Furthermore, the diaphragm must enable to use variable focus-skin distance, beginning with a minimal distance determined by the size and construction of the diaphragm and the rayproof container of the roentgen tube. Either a fixed distance — in this case 50 cm or more — or a varying focus-skin distance can be used as necessary in that technique where the focus-skin distance, except for the radiation intensity and filtration, even is depending on the size of the field and the depth of the focal lesion (2).

Except for this, such a universal diaphragm must enable to compress the body and thus to replace the compression tubes of diverse length and size of field, which otherwise are necessary for the treatment. It

[1] Submitted for publication, June 28, 1950.

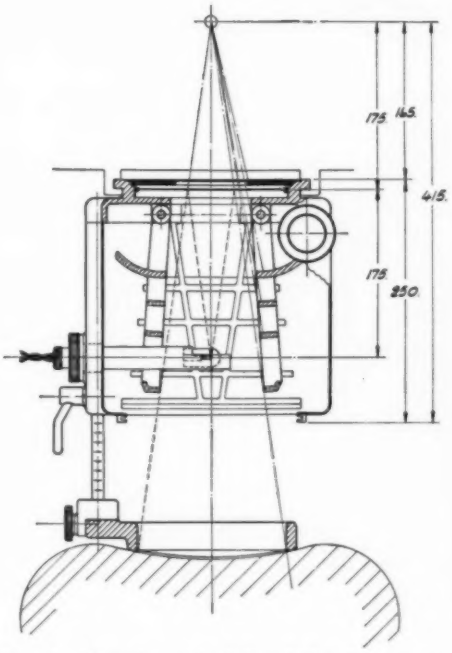

Fig. 1. Drawing principle of the diaphragm (distances in mm).

Fig. 2. The diaphragm attached to the Siemens protected container.

would be a great advantage if compression could be performed with lighting of the field at the same time. That gives a possibility to vary the field within the limits of the translucent compression plate.

When the compression plate is not in use, the adjustment of the focus-skin distance is controlled by an indicator-plate, which can be easily fixed to and removed from the distance-measuring rod of the diaphragm.

The roentgen therapy diaphragm shown here (Fig. 1—4), which serves the demands mentioned above, is constructed according to the principle of a step diaphragm. To reduce the size of the instrument from that published formerly, the lighting has been modified inasmuch as a plane mirror has been placed in front of the opening of the tube container. An electric low current lamp is used for lighting and is by means of a holder introduced in the beam in such a way that its distance from the mirror is identical to the distance from the roentgen tube focus to the mirror. Thus identity of the lighting and the roentgen beam is obtained. The

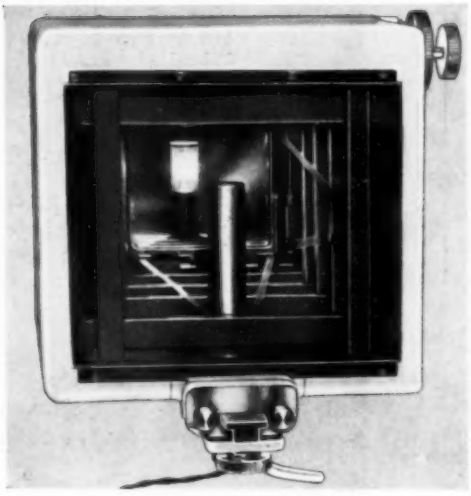

Fig. 3. The diaphragm from below with the steps and the light reflected on the mirror.

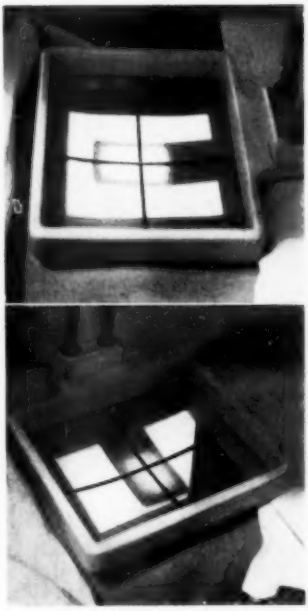

Fig. 4. The compression organ in function. Note the light area on the centre of the field.

shadow of the lamp holder itself falling on the field of treatment is made almost invisible by a direct lighting through a hole in the lamp holder.

By this universal diaphragm the reduction of the off-focal rays is considerably higher than by a simple disc-shaped diaphragm, or 8 per cent if even the slight absorption by the glass mirror is taken in account. Performed control measurements with the small ionization chambers of SIEVERT and with the dosimeter of Siemens show that the screening-off of the off-focal rays as well as the distinction of the field limits by this new step diaphragm is well agreeing with the values obtained by the diaphragm published formerly (1). In the daily work a more distinct field limitation is noted on patients during the skin reaction if the deep therapy diaphragm is used than by use of the ordinary lead rubber cover. The good distinction of the field limit is demonstrated on Fig. 5, showing multiple irradiation fields in a case of cerebral tumour, with intact non-epilated hair between the fields.

This new diaphragm for therapy, made by the Firm Järnh-Elema in Stockholm, has been in daily use at the Radiological Clinic in Eskils-

tuna since 1944, being attached to a Siemens tube container. Our experiences of it have been good. The construction has proved to be stable and lasting. The size of the diaphragm is seen on Fig. 1. By use of the mirror lighting as described above, the length of the diaphragm is depending on the distance from the focus to the opening of the roentgen tube container — for our apparatus 175 mm —. If used at the newly constructed Siemens small oil-isolated tube containers for therapy, this distance will be considerably less and consequently a diaphragm of similar construction will here be considerably shorter.

Fig. 5. Showing the good distinction of the field limits during the skin reaction.

As a rule in the deep roentgen therapy the author uses the diaphragm to control the beam's way in the human body. By this adjustment the diaphragm for *therapy* has shown itself as a perfect primary diaphragm for *diagnostics*. In direct connection to the treatment a film will be exposed by using a LYSHOLM grid and at the field on the skin a HERNHEISER lattice with one cm distance between the wires.

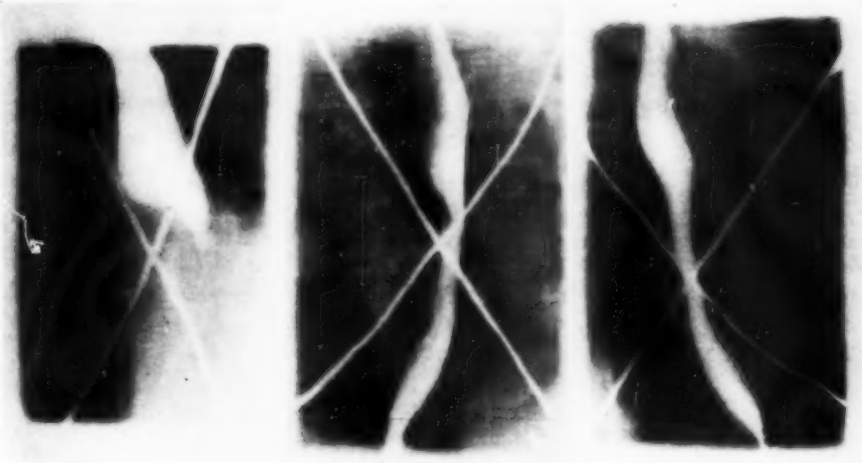

Fig. 6. The therapy-tube and therapy-diaphragm in diagnostic use. A case of oesophageal cancer before, during and after the treatment.
Exposure dates: 100 kv., 10 ma., filter 0.5 mm Cu + 1 mm Al, exposure of 4 seconds.

The positioning of the central beam in relation to the site of the focal lesion in the body will be marked on the film by an extra wire cross in the centre of the skin-field. Through this adjustment one gets a good and necessary information not only of the way of the beam through the body compared with that of the field on the skin, but also of the direction of the central beam against the focal lesion.

SUMMARY

The author describes a new construction of a deep therapy diaphragm formerly reported by him, designed as a universal diaphragm to replace the manual lead-rubber cover and the compression tubes which were needed in various sizes. The author notes the value of this diaphragm even for exposures with the therapy-tube to control the size and the direction of the beam and its relation to the focal lesion.

ZUSAMMENFASSUNG

Der Verfasser berichtet über eine Neukonstruktion der von ihm früher beschriebenen Therapieblende, welche die früher gebräuchliche Bleigummiabdeckung der Umgebung des Behandlungsfeldes und die verschiedenen grossen Kompressionstuben ersetzt. Der Verfasser hebt die Anwendbarkeit der Therapieblende für Exponierungen mit der Therapieröhre hervor, zur Kontrolle der Lage bzw. der Weite des Strahlenkegels und dessen Verhältnis zum Krankheitsherd.

RÉSUMÉ

L'auteur donne une description du principe de son nouveau diaphragme universel pour l'irradiation profonde par rayons roentgen, destiné à remplacer le revêtement en plomb sous caoutchouc et les »tubes de compression» de différentes longueurs et grandeurs de surface. L'auteur fait remarquer l'utilité de ce diaphragme de thérapie comme un diaphragme de diagnostic pour contrôler le passage des rayons roentgen pendant le traitement.

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PROCEEDINGS OF THE SIXTEENTH CONGRESS OF THE NORTHERN ASSOCIATION FOR MEDICAL RADIOLOGY

(NORDISK FÖRENING FÖR MEDICINSK RADIOLOGI) HELD IN STOCKHOLM, SWEDEN, ON JUNE 9TH—12TH, 1949.

Edited by CARL SANDSTRÖM, *Secretary-General.*

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Lelle Welin
Jane Westermark
Gogo Wickbom.

The Association voted to hold its next meeting in Aarhus, Denmark, in June, 1951.

The following officers were elected:

President:	Prof. Carl Krebs,	Denmark
Members of the Board:	Prof. P. Flemming-Møller,	»
	Dr. Kristian Overgaard,	»
	Dr. Kjeld Andersen,	»
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Deputy Members of the Board:	Dr. Chr. Baastrup,	Denmark
	Dr. Y. Lassila,	Finland
	Dr. J. Frimann-Dahl	Norway
	Prof. E. Lindgren	Sweden.
Auditors:	Dr. Bengt Holmgren	
	Mr. Carl Edemar.	
Deputy Auditors:	Dr. Sven R. Kjellberg,	
	Mr. C. B. Schmidt.	
To Honorary Members were elected:	Frank Adair, New York,	U. S. A.
	Max Cutler, Chicago,	U. S. A.
	Maurice Lenz, New York,	U. S. A.
	George Pack, New York,	U. S. A.
	Leo Rigler, Minneapolis,	U. S. A.
	Eugene Pendergrass, Philadelphia,	U. S. A.
	Wilhelm Stenström, Minneapolis,	U. S. A.
	William Edvard Chamberlain, Philadelphia,	U. S. A.
	W. V. Mayneord, London,	England.
	Ralston Paterson, Manchester,	England.
	Hugo Laurell, Uppsala,	Sweden.
	Rolf Sievert, Stockholm,	Sweden.

Dr. Sven R. Kjellberg was elected to assist the President in correcting the minutes.

THE PRESIDENT, PROF. ELIS BERVEN

in opening the Congress, spoke as follows:

Ladies and Gentlemen,

I should like to welcome all of you to the sixteenth meeting of the Northern Association for Medical Radiology.

First it is my painful duty to report the loss since our last meeting of several comrades who have passed to their eternal rest.

The world-famous English radiologist A. E. BARCLAY, our honorary member since 1933, died on April 27, 1949 at the age of 73 of our deadly enemy cancer. BARCLAY started his career as a practising roentgenologist in Manchester. When I visited England for the first time in 1919 and came to Manchester to study, he took care of the unknown little radiologist from Sweden in the most touching manner and with lavish hospitality, and did everything to make my visit as rewarding as possible. However, BARCLAY abandoned practical work early and devoted himself to teaching and research, first at Cambridge and later at Oxford, where he worked at the Nuffield Institute for Medical Research. For a generation he was one of the leading roentgen diagnosticians in England. He was among the promoters of the first International Congress of Radiology in London in 1925 and not long ago was appointed Vice President of the International Congress to be held in London next year. He published pioneer work in different branches of medical radiology. Most attention has been attracted by a work recently published by BARCLAY and his co-workers, demonstrating the existence of a mechanism of functional obstruction of certain parts of the renal vascular system. FORSSELL has written his obituary in a newspaper article.

RENÉ LEDOUX-LEBARD, also an honourary member since 1933, died in June, 1948, at the age of 69, likewise of cancer. He was a pupil of ANTOINE BÉCLÈRE, the FORSSELL of France, and well known and appreciated by Swedish radiologists since his visit in Stockholm in 1928. His doctorate thesis »La lutte contre le cancer» gave rise to the formation of the French Cancer Association in 1906. He was also one of the founders of La Societé de Radiologie and of the Journal de Radiologie et d'Électrologie. His most distinguished scientific works were a publication on the localization and extraction of projectiles, based on his experiences during the first World War, and one textbook on roentgen physics and one on roentgen technique. For over 25 years, up to his death, he held the chair of Clinical Radiology at the Medical Faculty in Paris. LEDOUX-LEBARD was an art lover and had a fine collection in particular of etchings and books. His influence on the development of radiology is well known and recognized all over the world, and his death is a severe loss to our science. (BELOT has written his obituary in Journal de Radiologie, Nr. 1, 1949.)

The Finnish radiologists have lost one member, MICHAEL ZALL, who died after a stomach operation at the age of 55 years. Following specialization in medical radiology and internal medicine, he became in 1936 physician and roentgenologist at the Kotka Municipal Hospital, where he remained until his death. I quote GÖSTA JANSSON: »Hs was a good worker, a good colleague, and a jolly good fellow. He was musical and hie virtuosity at the piano was frequently a source of great pleasure to his colleagues and friends.»

In Iceland GUNNLAUGUR CLAESSEN, the first and the most distinguished radiologist of his country, has died at the age of 66. His death resulted from a combination of asthma and a protracted infection of the upper respiratory tracts which his own powers of resistance were unable to overcome. FORSSELL has written his obituary in the Acta Radio-

logica. CLAESSEN was a central figure in the cultural life of Iceland and a great educator of his people. FORSSELL writes that »the history of his life and pioneer work is like a story taken directly from the old Icelandic sagas». CLAESSEN was a man of wellrounded education, and he spoke fluently and wrote in five languages besides his mother tongue. When in Sweden, he spoke pure, beautiful Swedish with little or no accent; in Denmark he spoke Danish beautifully. He was trained as a radiologist by FISCHER and FORSSELL and as early as 1914 he became chief of Iceland's first Roentgen Institute at the University with diagnostic, therapeutic, and light-therapy departments which were very well equipped for that time. Later he enlarged these departments at the same time as he kept the technical equipment up to date and of first quality in every respect. In 1928 he took his doctorate in medicine in Sweden with a thesis entitled »the Diagnosis of Echinococcus Tumours», and a year later he was appointed teacher of radiology at the University of Reykjavik. His greatest work was his »Röntgendiagnostik, Vejledning for Læger og Studerende», a second edition of which was published in 1946. It has been translated into English. CLAESSEN fought energetically against favus, endemic in Iceland, and in our Acta he has described his method of treating this disease by roentgen rays. Side by side with his radiological work he was active in social hygiene and general medicine, in both of which his achievements were valued and effective. He was for a long period one of the associate editors of Acta Radiologica. His death is a great loss not only to Iceland but also to medical radiology as a whole.

In Norway A. G. SCHIANDER has passed away at the age of 67. He studied radiology under HEYERDAHL and as early as 1917 he established a private roentgen diagnostic department in Oslo. He took part in the formation of the Northern Association for Medical Radiology in 1919 and the Norwegian Association in 1920, of which he was Secretary for many years. His extensive practice left him no opportunity for scientific work, but he was a faithful guest at all our meetings and an excellent secretary. His beautiful home with its magnificent view over Oslo Fjord was always hospitably open to his friends.

TRYGGVE KROGDAHL died at the age of 45 in an accident. After obtaining his degree he secured a thorough training in radiology by serving in a number of radiological departments and in 1943 opened his own roentgen institute. He has published works on the anatomy and pathology of the unco-vertebral joints in Acta.

Swedish radiology has suffered heavy losses during this year.

DAG BERNHARD CARLSTEN, a dear friend of all of us, died at the age of 61 of a erebral haemorrhage following his recovery from pneumonia. He was one of FORSSELL's earliest pupils and the first of these to take his doctor's degree, as early as 1917 with a thesis entitled »Zur Röntgenologie der Nasenhöhle», published in Nordisk Tidskrift för Oto-Laryngologi. He devoted his whole life to the development of the radiological department at the Malmö General Hospital and in 1942 he had the pleasure of being able to open a completely modern diagnostic and therapeutic department. Side by side with his pressing daily routine he also found the time to continue his scientific work. He served faithfully as Treasurer of the Swedish Association for Medical Radiology for over 20 years. All of us liked DAG BERNHARD for his refreshing, sometimes rather burlesque humour, but also for his deep understanding of everything human and for his love of life. His death has left a large vacuum in the hearts of his friends. ÅKERLUND has written his obituary in Acta Radiologica.

When HANS HELLMER, Professor of Roentgen Diagnostics at the University of Lund, died of cancer on March 23 of this year at the age of only 51, Swedish radiology suffered a very heavy loss. He was taken from us at the height of his powers as physician, teacher, and scientist. At the age of 23, HELLMER began his training under FORSSELL, to whom he was deeply devoted. The young man was a soul of fire; OLLE OLSSON writes in his obituary: »He was an elemental force, ungovernable, incalculable, ruthless, but

with the results of his activity always under control. His capacity for work was unbelievable, his demands imperative.» This describes the man. HELLMER organized the roentgen diagnostic department at Lund and brought it to a high degree of completion. He enjoyed the undivided confidence and admiration of his colleagues and his pupils. He carried on intensive research, with which we are all familiar, embracing among other things mucous membrane relief, skeletal and urinary tract diagnostics, and his important works on intestinal intussusception in children. HELLMER was also deeply interested in and devoted much time to his teaching activities, while as physician he tried to come into direct personal contact with his patients, a contact which he considered necessary for good diagnostic work.

In spite of severe roentgen injury to both hands which at times caused him great pain and led to the amputation of several fingers, he worked on with unquenchable energy. He endured his last severe illness with sublime stoicism, and with a philosopher's calm he awaited the merciful release of death. In him we have lost a great man.

During the first struggling years, the radiologists had no real home. Radiological departments were housed in a few rooms in medical or surgical clinics, in cellars or attics. Roentgen diagnosticians were called hospital photographers, and when in 1896 HOLGER MYGIND in Copenhagen demonstrated some roentgen pictures, a Professor of Surgery is said by BAASTRUP to have remarked, »Ja, det her kan ju være morsomt, men nogen praktisk Betydning kan det da aldrig faa» (well, this may be amusing but it will never have any practical significance) and a few years later a Swedish physician considered radiotherapy to be scientific humbug. I have since had the pleasure of treating him and curing a condition which was, to be sure, very simple — cancer of the skin of the face — but then at any rate he was satisfied with roentgen therapy. ROVSING, the great Danish surgeon, considered radium very good — for warts, but after all he too became an advocate of radiotherapy.

At that time we were obliged to report on our work to our colleagues at the medical and surgical congresses. We also had to publish our experiences in foreign, particularly German, periodicals, where they were drowned in the flood of literature. The first world war with its isolation of the neutral countries made it still more difficult for us to publish the results of our scientific work.

At the Northern Surgical Congress in Gothenburg in 1916, the possibilities of development of Northern radiology were made the subject of much discussion by the three great men of that time, FISCHER, FORSSELL, and HEYERDAHL. Thereafter plans gradually ripened to establish a joint periodical for all the Northern countries, in which the part played by these countries in the development of medical radiology would appear to greater advantage as well as to form a Northern Association for Medical Radiology for the promotion of radiological research and the union of Northern radiologists in friendly cooperation.

The second aim was attained on July 2, 1919, when the Northern Association for Medical Radiology was ceremoniously founded in Oslo in the banquet hall of the University. The first one was attained a few years later, when on July 25, 1921, the first number of Acta radiologica appeared.

These two events constitute the foundation of the proud present-day building of Northern radiology. In the 31 volumes with 77 supplements of Acta which have appeared in the course of the past 28 years, we can follow the history of the glorious development of Northern radiology, bearing witness to lively scientific activity.

I should like to give a brief résumé of the past years. HEYERDAHL summoned the radiologists to the first Northern meeting 30 years ago. We meet today, as has been said, for the sixteenth time. The first meeting was attended by 2 Danes, 8 Swedes, and

the 7 Norwegian radiologists of the time, 4 from Oslo and 3 from the surrounding area — a total of 17. 210 active participants have come to our meeting today. That first meeting was held in connection with the congresses of the Northern Surgical and Gynecological Associations on July 3rd and 4th. On July 5th the radiologists held their own meeting in the roentgen diagnostics demonstration room of the University Hospital, dimensions 4 m × 3 m, which was ample for all 17 radiologists and a few interested surgeons. In the morning FORSSELL lectured on the roentgen diagnosis of gallstones, »to which», according to the minutes, »BAASTRUP added a few supplementary remarks». ÅKERLUND lectured on bulb deformities in duodenal wounds, HEYMAN on the results obtained in radium treatment of cancer of the uterus after 4 years' observation, and BERVEN on radiological treatment of cancer vulvae. In the afternoon there were brief demonstrations by FORSSELL, HEYERDAHL, STRÖM, and ÅKERLUND. It was decided that meetings should be held alternate years, preferably in conjunction with the surgical and gynecological congresses, and that the President should be appointed by the radiological association of the country where the next meeting was to be held. BAASTRUP was appointed General Secretary and carried this heavy burden until 1936.

The banquet — and it *was* a banquet in spite of the prohibition — was held in HEYERDAHL's dining room, where there was plenty of room and spirits for all of us.

Such was the beginning of 30 years of fruitful cooperation among the Northern radiologists, years which were to see the forming of many valuable friendships. In Sweden, Norway, and Denmark 4 meetings have been held in each country, and in Finland 3. The first meeting was, as mentioned, held in 1919, in Oslo, and so was the sixth in 1929, the tenth in 1939, all with HEYERDAHL as President, and the fifteenth in 1948 with DALE as President. In Copenhagen were held the second meeting in 1921 with FISCHER as President, the fifth in 1927 with PANNER as President, and the ninth and thirteenth in 1938 and 1946, respectively, with FLEMMING MØLLER as President. The third, seventh, and eleventh were held in Stockholm in 1923, 1933, and 1941, respectively, with FORSSELL as President, and the twelfth in 1942 in Lund with EDLING as President. The fourth and the eighth meetings in 1925 and 1936 respectively, with WETTERSTRAND as President, and the fourteenth in 1947 with JANSSON as President were held in Helsingfors.

We can read the history of the development of Northern radiology during these 30 years in Acta radiologica, where the minutes of the meetings and most of the lectures delivered have been published. Radiology has now developed to such an extent that it is impossible for *one* man alone to follow and to have a thorough grasp of all the results of current research. We are hard pressed for both time and strength, and the progress of our science threatens to outstrip us.

Hence it is necessary by means of these recurrent meetings to report on new methods, new technical improvements, and results obtained. In the hope that this meeting will be a worthy successor to its foregoers I call the sixteenth meeting of the Northern Association for Medical Radiology to order.

SCIENTIFIC TRANSACTIONS.

Lectures on therapy.

E. BERVEN: King Gustaf V's Jubilee Clinic (comprising the Radiumhemmet, the Institute of Radiopathology and the Institute of Radiophysics).

J. HEYMAN: Some aspects on the presentation of therapeutic results.

R. SIEVERT: A new principle for roentgen irradiation. (See the following publications: »A roentgen apparatus for intense roentgen radiation of short duration intended

for biophysical research work and for special treatment purposes» by R. SIEVERT, Acta radiol. XXXIII (1950), 328, and »A method of concentrating roentgen rays for deep therapy» by B. LINDELL, R. SIEVERT and T. WAHLBERG, Acta radiol. XXXIII (1950), 344.)

R. SIEVERT: Measurement of the normal radioactivity of the human body. Will be published in Acta radiol.

H. L. KOTTMEIER: Some aspects on the irradiation of carcinoma of the uterine cervix. Will be published in Acta radiol.

Methods of treatment and results at the Radiumhemmet:

O. HALLBERG: Carcinoma of the hypopharynx.
O. MORALES: Carcinoma of the oesophagus.
H. AHLBOM: Malignant tumours of the testis.
H. AHLBOM: Mucous- and salivary-gland tumours.
S. HULTBERG: Malignant tumours of the maxilla.
S. HULTBERG: Lymphogranulomatosis maligna.
B. SYLVÉN: Malignant melanomas. Acta radiol. XXXII (1949), 33.
G. FORSSMAN: Giant-cell tumours of the skeletal system.
S. NORDLANDER: Presentation of some interesting case histories.

Demonstration of:

The therapy departments of the Radiumhemmet.
The Institute of Radiophysics and its newly built High Voltage Laboratory.
The Institute of Radiopathology.

SVEN HULTBERG: Short-distance low-voltage roentgen therapy of inflammatory conditions in the tonsils. Acta radiol. XXXII (1949), 66.

F. WACHSMANN: Ausblick auf die Anwendungsmöglichkeiten der Elektronenschleuder in der Medizin und bisherige Versuchsergebnisse mit ultraharten Strahlungen. Acta radiol. XXXII (1949), 145.

ERNST INGE GYNNING: Some points of view on the rotation treatment of cancer of the hypopharynx. Will be published (in more details) in Acta radiol.

OLLE HALLBERG: Further experiences with palliative testosterone treatment of cancer mammae.

C. KREBS, HOWARD NIELSEN and POUL E. ANDERSEN: Rotation treatment of cancer of the esophagus. A clinical material. Acta radiol. XXXII (1949), 304.

MAGNUS STRANDQVIST: Therapy tests with radioactive phosphorus.

L.-G. LARSSON: A study on sarcoidosis with special reference to the radiological treatment.

R. WEYDE: Naevus epithelioma cylindromatosus transmitted through four generations. Nord. Med. 44 (1950), 1249.

W. RATJEN: Studies on the permeability of erythrocytes after roentgen treatment.

H. MOSSBERG: 1. Some aspects on the roentgen treatment of polycythaemia vera. Will be published in Acta radiol. — 2. Platelet values in personnel engaged in roentgen diagnostic work. Acta radiol. XXXIV (1950), 186.

A. EGMARK: An unregarded risk moment in handling radioactive solutions.

P. JACOBY: 5 years' results with pre- and post-operative roentgen treatment of cancer of the breast. Acta radiol. XXXIV (1950), 453.

P. ANDERSEN: Testosterone propionate in the treatment of advanced carcinoma of the breast. Acta radiol. XXXII (1949), 159.

Lectures on roentgen diagnosis.

Å. Åkerlund: Intramural small-cystic diverticulosis of the gallbladder. Acta radiol. XXXIII (1950), 147.

O. Norman: Cholangiographic demonstration of stones in the intrahepatic bile ducts. Will be published in Acta radiol.

J. Frimann-Dahl: Roentgen examination of mesenteric thrombosis. Will be published im Am. J. Roentgenol.

G. Thomsen: Congenital short esophagus in infancy and childhood. Will be published in Acta radiol.

Th. Rosendal: Neonatal occlusion on account of abnormity in the upper part of the intestine.

S. Rennaes and R. Bull Engelstad: Attempts at gastric examination by photofluorographic methods. Acta radiol. XXXIII (1950), 49.

Arne W. Claussen: Submucous lipoma of colon. Nord. med. 42 (1949), 1936.

K. Lindblom: Roentgenographic studies of hydronephrosis due to obstruction at the uretero-pelvic junction. Acta radiol. XXXII (1949), 113.

F. Knutsson: The myelogram following operation for herniated disc. Acta radiol. XXXII (1949), 60.

T. Denstad: The resorption of abrodil in myelography. Acta radiol. XXXII (1949), 428.

Olle Olsson: Further experimental and clinical studies of contrast media for cerebral angiography.

I. Wickbom: Angiography in post-traumatic intracranial haemorrhages. Acta radiol. XXXII (1949), 249.

Hans G. Skarby and C. Johansson: Elsberg's symptom. Will be published in Acta radiol.

J. Torgersen: A roentgenological study of the metopic suture. Acta radicl. 33 (1950), 1.

B. Nordmark: Pressure changes in the sella turcica in the presence of glioma in the cerebral hemispheres. Acta radiol. XXXII (1949), 461.

G. Jönsson and B. Brodén: Selective angiocardiography. Acta radiol. XXXII (1949), 486.

Carl Wegelius and Johan Lind: Angiocardiografic studies on the human foetal circulation. Pediatrics 4 (1949), 391.

Å. Gidlund: 1. A new apparatus for direct cineroentgenography. Acta radiol. XXXII (1949), 81. — 2. Angiographic circulatory studies by means of cineroentgenography.

B. Brodén and G. Jönsson: The technical problems connected with thoracic aortography and the various risks involved in the use of the method. Acta radiol. XXXII (1949), 498.

F. Ulfsparre: Anomalies of the superior vena cava in congenital heart defects.

E. Salén: A phlebographic survey of constrictive processes in the superior vena cava-area and of accompanying changes in the collateral circulation. Will be published in Acta radiol.

R. Weyde: Further experiences with abdominal aortography. Will be published (in more details) in Acta radiol.

S. R. Kjellberg: The heart volume in rest and its relation to the frequency of the pulse and to the blood volume. (See Acta radiol. XXXI (1949), 113; Cardiologia 14 (1949), 371 & Acta physiol. Scandinav. 19 (1949), 146 & 152.)

ULF RUDHE: The condition of the cardiac volume during pregnancy. Acta radiol. XXXI (1949), 123.

TURE ANDERSSON: Electrokymographic recording of auricular movements. Acta radiol. XXXII (1949), 121.

Y. PAATERO: A new tomographical method for radiographing curved outer surfaces. Acta radiol. XXXII (1949), 177.

A. SONESSON: 1. The roentgen diagnosis of adamantinomas of the jaws. — 2. The roentgen diagnosis of central fibromas and fibromyxomas of the jaws.

Both lectures are included in the publication »Odontogenic Cysts and Cystic Tumours of the Jaws. A Roentgen-diagnostic and Patho-anatomic Study.» Acta radiol. Suppl. LXXXI (1950).

P. BJERRE HANSEN: The relationship of Hand-Schüller-Christian's disease, Letterer-Siwe's disease and the eosinophilic granulomas of bone (with report of five cases). Acta radiol. XXXII (1949), 89.

A. ENGSTRÖM: Physical-chemical investigations of nerve- and muscle-fibers by micro-radiography. Acta radiol. XXXI (1949), 503. (See also »Use of soft X-rays in the essay of biological material» in »Progress in Biophysics and Biophysical Chemistry», Ed. Butler & Randall, Butterworth Scientific Publ. Co., London.)

R. STEINERT: The protective power of roentgen gloves. Will be published in Acta radiol. XXXV (1951).

S. RIBBING: A roentgen examination chair. Sv. Läkartidn. 46 (1949), 1523. (Published in Swedish.)

Å. GIDLUND: New instruments for bronchography. Acta radiol. XXXIII (1950), 421.

O. MORALES: Further studies with Umbradil-Viskös. Acta radiol. XXXII (1949), 317.

L. LÖNNERBLAD: Two types of tuberculosis often neglected. Published (in more details) in Acta radiol. XXXIV (1950), 501, under the title »The value of a total population chest survey in the campaign against tuberculosis».

OVE MATTSSON: An untypical filmfault. Published (in more details) in Acta radiol. XXXIV (1950), 166.

C. E. NYLUND: Two luetic cases with pulmonary changes.

I. HESSÉN: The roentgen diagnostic procedure in evaluating the normal amount of fluid in the pleural cavity. Will be published (in more details) in Acta radiol.

Corrigendum

ad

MULTIPLE MYELOMA

by

Lars Anda

In the June 1950 issue of the Acta Radiologica, on page 516, I have quoted some work on multiple myeloma, reported by GARLAND and KENNEDY in 1947. In the last sentence the important word »not» is accidentally omitted. The authors' experience was that the disease of multiple myeloma was *not* so radiosensitive as generally believed.